TRANSCUTANEOUS BILIRUBIN NOMOGRAM IN LATE PRETERM FOR PREDICTION OF SIGNIFICANT HYPERBILIRUBINAEMIA

DOCTORATE IN MEDICINE (NEONATOLOGY)

OF

DR. NELBY GEORGE MATHEW

DEPARTMENT OF NEONATOLOGY

CHRISTIAN MEDICAL COLLEGE

VELLORE – 632 004

Certification

This is to certify that the dissertation entitled "**TRANSCUTANEOUS BILIRUBIN NOMOGRAM IN LATE PRETERM FOR PREDICTION OF SIGNIFICANT HYPERBILIRUBINAEMIA**" is a bonafide work done by **DR.NELBY GEORGE MATHEW** in the Department of Neonatology, Christian Medical College, Vellore, in partial fulfilment of the Tamil Nadu Dr. M.G.R. Medical University rules and regulations for award of Doctorate in Medicine (branch XI) Neonatology during the academic year 2012-2015.

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Sub: **Fluid Research grant project:**
Transcutaneous bilirubin nomogram in late preterm for prediction of significant hyperbilirubinaemia
Dr. Nelby George Mathew, PG Student, Dr. Santhanam Sridhar. S,
Dr. Abiramalatha, Dr. Niranjan Thomas, Dr. Atanu Kumar Jana, Neonatology, Mrs. Visalakshi J, Biostatistics, CMC, Vellore.

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Dear Dr. Nelby George Mathew,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project entitled "Transcutaneous bilirubin nomogram in late preterm for prediction of significant hyperbilirubinaemia" on December 4th, 2013.

The Committees reviewed the following documents:

1. IRB application format
2. Curriculum Vitae' Drs. Nelby George Mathew, Santhanam Sridhar S, Visalakshi J, Abiramalatha, Niranjan Thomas, Atanu Kumar Jana.
3. Consent form (English & Tamil)
4. No of documents 1-3

The following Institutional Review Board (Blue, Research & Ethics Committee) members were present at the meeting held on December 4th, 2013in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore 632002.

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We approve the project to be conducted as presented.

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The Institutional Ethics Committee expects to be informed about the progress of the project, any **adverse events** occurring in the course of the project, any **amendments in the protocol and the patient information / informed consent**. On completion of the study you are expected to submit a copy of the **final report**. Respective forms can be downloaded from the following link: http://172.16.11.136/Research/IRB_Polices.html in the CMC Intranet and in the CMC website link address: http://www.cmch-vellore.edu/static/research/Index.html.

Fluid Grant Allocation:

A sum of 5,000/- INR (Rupees Five Thousand only) will be granted for 1 year.

Yours sincerely

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

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CONTENTS

INTRODUCTION

Jaundice is the clinical manifestation of hyperbilirubinemia and is due to the deposition of bilirubin on the skin, subcutaneous tissue and the sclera(1). Neonatal jaundice is clinically apparent at a serum level above 5 mg /dl. Neonatal hyperbilirubinemia is very common with an incidence of 60 % in healthy term babies and most preterm babies, but only a few of among these babies have significant underlying disease(2)(3). The term jaundice was taken from the French word “jaune”, meaning yellow and hyperbilirubinemia is also referred to as icterus which came from Greek literature.

Newborn are prone for hyperbilirubinemia due to increased bilirubin production because of increased RBC destruction, defective bilirubin elimination due to defective hepatic uptake, defective conjugation attributed to immaturity of newborn and also increased entero-hepatic circulation. Preterm babies are more prone for hyperbilirubinemia compared to term babies.

Late preterm babies are those born between 34 0/7 weeks of gestation (239 days) and36 6/7 weeks gestation (259 days) calculated from the first day of mother’s last menstrual period (4). Late preterm infants born at 36 weeks haveapproximately 8 times increased risk of developing total serum bilirubin(TSB)more than 20 mg/dl as compared to term babies born at 41- 42 weeks(5).The increased incidence of hyperbilirubinemia in late preterm infants is mainly due to decreased Uridinediphosphateglucoronosyltransferase 1A1UGT1A1 enzyme activity which is the enzyme concerned with the

conjugation of bilirubin and making it water soluble for its excretion (6)(7) as late preterm babies were found to have similar degree of erythrocyte turnover and heme degradation as compared to their term counterparts. Late preterm, because of their immaturity, fail to achieve consistent nutritive breast feeding because of less effective sucking and swallowing which contributes to exaggerated hyperbilirubinemia.

Late preterm babies are disproportionately over represented in the US Pilot Kernicterus registry and late preterm babies shows signs of bilirubin neurotoxicity at an earlier age suggesting a greater vulnerability of late preterm babies for bilirubin induced brain injury (8).

Most neonatal guidelines including the AAP guidelines regarding management of neonatal hyperbilirubinemia considers new born more than 35 weeks in a single group and treating late preterm as a separate entity is not considered .

Different methods of assessment of hyperbilirubinemia are clinical assessment, serum bilirubin estimation and by transcutaneous bilirubin (TcB) estimation.

Many studies have shown that clinical estimation of serum bilirubin as a screening tool is not reliable and may fail to detect significant neonatal hyperbilirubinemia before discharge and may lead to inadequate follow up(9)(10)(11).

Hour specific serum total bilirubin nomogram by Bhutani et al (12)is used widely to predict the risk of significant hyperbilrubinemia and also for

identifying the need for additional evaluation(13).The problem with serum bilirubin estimation is it is an invasive procedure.

To circumvent the problem of invasive procedure, transcutaneous bilirubin estimation was introduced. Transcutaneous bilirubin estimation is a better screening method when compared to visual estimate (14)(11).

Study conducted in our own institute showed good correlation between serum bilirubin value and transcutaneous bilirubin value especially among preterm babies.

Currently transcutaneous bilirubin nomograms are available for different regions of the world covering different populations. None of the nomograms differentiated late preterm as aseparate entity while constructing nomograms.

Our study was done with the intention of constructing a transcutaneous bilirubin nomogram exclusively for late preterm babies as a first step in seeing the normal trend of bilirubin rise in late preterm babies. Our secondary objective was to see the correlation between the serum bilirubin values of late preterm which was obtained as part of unit protocol to the corresponding transcutaneous value.

AIMS AND OBJECTIVES

Aim:

To construct transcutaneous bilirubin (TcB)nomogramfor late preterm babies.

Objectives:

1. Primary Objective

    To construct a nomogram for TcB values in late preterm babies over the first 120 hours of life.

2. Secondary Objective

    To assess the correlation and agreement between the transcutaneous bilirubin and serum bilirubin values

    To construct a regression equation (if possible) to predict serum bilirubin from transcutaneous bilirubin level in late preterm babies.

REVIEW OF LITERATURE

Jaundice

Bilirubin is the break down product of heme metabolism which imparts yellow colour to skin and subcutaneous tissues.

Increase in bilirubin level , hyperbilirubinemia, manifests clinically as jaundice which is a yellowish pigmentation of the mucous membranes, skin and the conjunctiva(1). Adults and older children appear jaundiced once the serum bilirubin value is more than 3md/dl(15).New-born babies appear jaundiced when serum bilirubin is more than 5 mg/dl and around 60 % of healthy term newborns and most of the preterm babies have clinical jaundice in the first week, but only a few of these babies have significant underlying disease(2)(3).

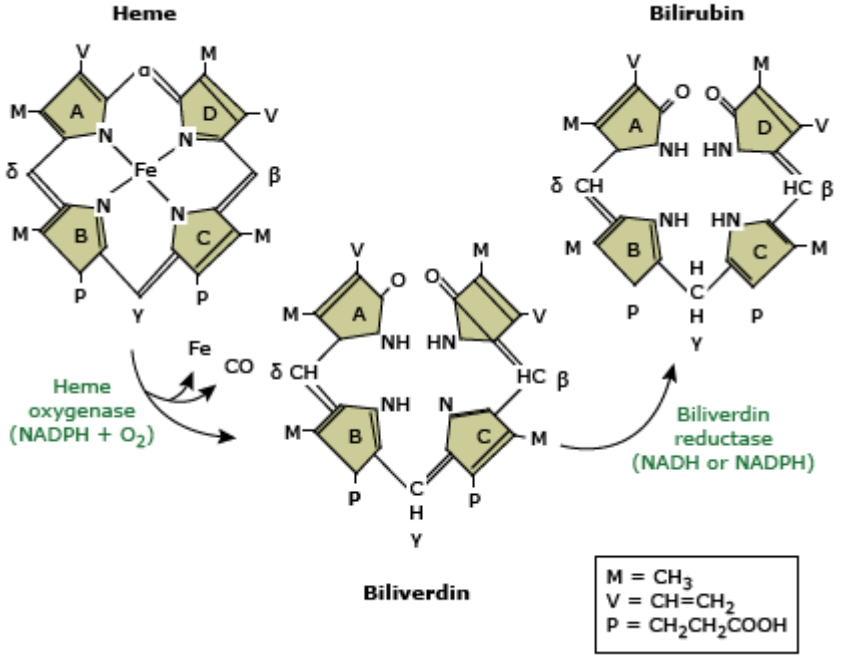
Bilirubin metabolism

Bilirubin is the break down product of heme metabolism.Heme is present in hemoglobin, myoglobin, cytochromes, catalase, peroxidase and tryptophan pyrolase. Eighty percent of the daily bilirubin production is derived from hemoglobin(16)and the other 20% is derived from other hemoproteins and a rapidly turning-over small pool of free heme. In an adult, after 120 days of lifespan, red blood cells are broken down and hemoglobin is released which finally gets converted to bilirubin. This explains why any condition leading on to excess hemolysis can lead on to hyperbilirubinemia

The haemoglobin released from RBCs is further broken down to haem and globin. Haem consists of four pyrrole rings joined by carbon bridges and has a central iron atom. Haem degrades to form bilirubin and in the process releases iron and CO .Measurement of intrinsic CO production has been found to be useful to quantify bilirubin production(17). The globin may be utilised as such for the formation of haemoglobin or degraded to individual aminoacids.

Bilirubin is formed by the sequential catalytic degradation of heme, mediated by two groups of enzymes-hemeoxygenase and biliverdinreductase. Biliverdinis produced by the opening up of porphyrin ring in the reticuloendothelial tissue by the enzyme hemeoxygenase. This reaction releases one molecule of CO which is excreted through lungs. Biliverdin is acted upon by the enzyme biliverdinreductase and gets converted to bilirubin.

Conversion Of Heme To Bilirubin (Figure -1)



Hemeoxygenase is present in high concentration in the reticuloendithelial system and is the rate limiting step in bilirubin production (18).

Bilirubin formed is non-polar,water insoluble and needs to be attached to serum albumin for transportation to the liver.This albumin bilirubin complex forms the Indirect Bilirubin or Unconjugated Bilirubin.Bilirubin bound to albumin usually does not cross blood brain barrier and hence thought to be nontoxic but once the hyperbilirubinemia exceeds albumin`s ability to bind to the bilirubin, then unbound unconjugated bilirubin becomes toxic.

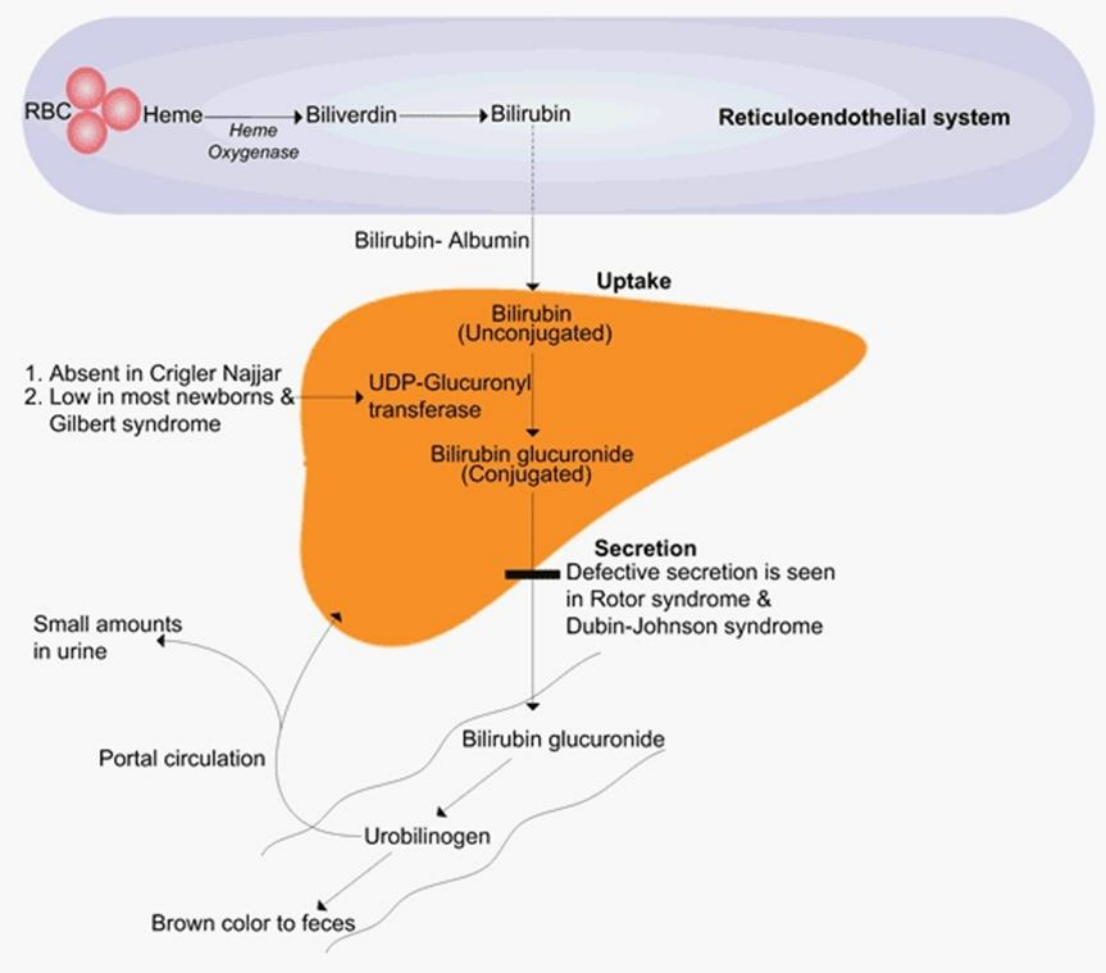
Uptake of bilirubin by liver cells: After dissociation from albumin,lipophylic bilirubin crosses the hepatocyte plasma membrane and binds to cytoplasmic ligandin to be transported to the endoplasmic reticulum

Conjugation of bilirubin with glucuronic acid: Unconjugated bilirubin has to be converted to water soluble form (conjugated bilirubin) before excretion and the conjugation occurs in the smooth endoplasmic reticulum by the enzyme uridinediphosphogluconurateglucoronosyltransferase(UGT) to form bilirubin monoglucuronide which if further undergoes conjugation forms bilirubin diglucuronide and both these conjugated forms of bilirubin can be excreted easily into the bile canaliculi .UGT 1A1 enzyme activity depends on the developmental maturation of the baby. The activity is around 0.1 % at 17 - 30 weeks and reaches 1% of adult value by 30-40 weeks. Post-delivery, the maturation of UGT1A1 is hastened and reaches adult value by 14 weeks of life.

Excretion of conjugated bilirubin into bile: Conjugated bilirubin being water soluble is excreted into the bile and it reaches the small intestine

Once conjugated bilirubin reaches the intestine, glucuronides are removed by the intestinal bacteria, and it is converted to urobilinogen which is further converted to stercobilinogen and is excreted in stool. Some urobilinogen is absorbed into the systemic circulation and is eliminated in the urine. Some conjugated bilirubin gets reconverted to unconjugated bilirubin by the intestinal enzyme β-glucorunidase and this unconjugated bilirubin is reabsorbed to systemic circulation which forms the entero hepatic circulation.(19)(20).

BILIRUBIN METABOLISM (Figure -2)



Reasons for high suseptibilty of neonate's forhyperbilirubenemia

Neonates are more prone to hyperbilirubinemia and this physiological hyperbilirubinemia is due to immaturity in every step of bilirubin metabolism:

1) Increased bilirubin production because of

a) Increased hemeoglobin per kilogram and the short survival of RBC

b)Increased ineffective erythropoiesis and increased production of nonhemeoglobinhemeproduction.

2) Decreased uptake of bilirubin since plasma binding ligandin levels are low

3) Decreased conjugation and decreased hepatic excretion of bilirubin also contributes to the physiological hyperbilirubinemia in new born.

4) Increasedenterohepatic circulation because of increased level of β glucoronidase, more of monoglucoronide instead of diglucoronide, decreased colonisation with intestinal bacteria and decreased gut motility (19).

Bilirubin toxicity

High bilirubin level is dangerous because unconjugated bilirubin which is not bound to albumin can cross the blood brain barrier.The deposition of bilirubin in the brain can cause acute bilirubin encephalopathy with later development of kernicterus. Kernicterus refers to deposition of unconjugated bilirubin in the brain with subsequent damage and scarring of the basal ganglia and the brain stem nuclei(21). If unbound serum bilirubin concentration exceeds the binding capacity of albumin, this unbound lipid soluble bilirubin crosses the blood brain barrier .If there is a damage to blood brain barrier as in conditions like asphyxia, hypoxia, acidosis, hypoperfusion, sepsis or hyperosmolality even albumin bound bilirubin can cross the blood brain barrier(22).

The exact bilirubin concentration which is associated with kernicterus is not exactly determined(2).Toxicity level depends on various factors like maturation of the baby,ethnic group ,and the presence of haemolytic disease. Risk of bilirubin toxicity is negligible in a healthy term new born without haemolysis(23),The physician should be concerned if bilirubin level goes above

25 mg/dl (2)(22)(24) and in haemolytic disease, if the serum bilirubin level goes above 20 mg/dl (2)(22)

Late preterm babies are more prone for hyperbilirubinemia and also more profound neurotoxicity even at the same bilirubin level as compared to term babies. Studies have identified late preterm gestation as an important recognised cause for severe hyperbilirubinemia(25) and kernicterus (26)(27).One common cause of significant hyperbilirubinemia in late preterm is that they are often cared in normal newborn nurseries and care givers often overlooks the high risk of late preterm developing hyperbilirubinemia while in reality the bilirubin conjugating mechanism is immature as compared to term babies placing them at high risk of developing significant hyperbilirubinemia. Late preterm babies are approximately eight times more prone for hyperbilirubinemia as compared to term babies; a baby born at 36 weeks has 5.2% chance of developing hyperbilirubinemia as compared to 0.7% incidence in babies born at 41 weeks.

Every effort should be made to prevent development of acute bilirubin encephalopathy and later development of kernicterus.The key elements to prevent hyperbilirubinemia induced brain injury is assessment of the risk factors for hyperbilirubinemia ,timely follow up of -babies and effective treatment of hyperbilirubinemia.The main modes of teatment of hyperbilirubinemia are phototherapy and exchange transfusion when bilirubin level is dangerously high. Total serum bilirubin (TSB) or transcutaneous bilirubin (TcB) measured at more than 18 hours of life combined with assessment of risk factors significantly

improves the ability to predict subsequent development of hyperbilirubinemia(28).

Late preterm babies

Late preterm refers to babies born between 34 weeks and 36 weeks and 6 days(4) . The term “near term” was replaced by “late preterm” as near term wrongly implies that these babies are almost term and need only the routine neonatal care(29).When compared with term babies, these babies have higher mortality and morbidity because of their relative physiological and metabolic immaturity(30)(31)(32).As per data from the USA, inspite of great efforts to decrease the incidence of preterm births, the incidence of preterm delivery is increasing. It has increased from 9.4% in 1981 to 12.3% in 2003(33)(34).The American College of Obstetricians and Gynaecologists (ACOG) suggests that the reason for increase of preterm birth rates is due to the dramatic rise in late preterm births(35). The exact incidence of late preterm babies in Indian population is lacking. An Indian study by Amarjeet S Wagh et al done in south India comparing the neonatal morbidities of late preterm with term born babies found .the incidence of preterm births was15.6 %of whom 8.9 percentage of babies were late preterm(36).Late preterm babies behave differently from term babies and have significantly high incidence of morbidity in the immediate neonatal period, increased incidence of readmission and may be at increased risk of long term neurodevelopmental impairment.

Late preterm babies are more prone to have a high serum bilirubin level because of the immaturity of the hepatic bilirubin conjugation pathway (37).Incidence of increased incidence of hyperbiliribinemia in late preterm varies in different studies. According to the study by Sarici SU et al, the incidence of significant hyperbilirubinemia requiring phototherapy in term babies was 10.5%,and in late preterm was 25.3%(38).Studies by Amarjeet S Wagh et al and Wang et al also revealed incidence of hyperbilirubinemia needing phototherapy among late preterm to be more than 50 %.(30)(36) Incidence of bilirubin induced brain injury and kernicterus are more for late preterm at a given bilirubin value compared to the term counterpart attributed to the immaturity of the blood brain barrier, low circulating albumin level and an increased incidence of concurrent illness(8)(39).

Hyperbilirubinemia is the most common cause of readmission for late preterm babies(8).Late preterm babies appear to have a similar degree of red blood cell turn over and heme degradation when compared to term babies, but have lower UDP glucuronosyltransferase 1 family, polypeptide A1(UGT1A1) enzyme activity(39).There is a rapid postnatal increase in the UGT1A1 activity in term babies, but this maturation is slower in late preterm babies(6).In late preterm babies, establishment of feeds is delayed due to delayed development of coordinated sucking and swallowing, which may lead to delayed successful breast feeding, dehydration and poor weight gain in the immediate post natal period. Delayed establishment of feeds may lead to increased enterohepatic

recirculation of bilirubin and hence cause an increase in serum bilirubin level(40)(41).

Assessment of hyperbilirubinemia

Different methods of assessment of hyperbilirubinemia are clinical assessment, serum bilirubin estimation and transcutaneous bilirubin estimation.

Clinical assessment of hyperbilirubinemia

The principle behind the clinical assessment of jaundice is that there exists a clear semi quantitative relation between the yellowness of the skin and the TSB value.Kramers rule was used as a guide for the level of jaundice.Kramers rule states that if Head & neck are jaundiced,it indicates serum bilirubin (SBR) of 100 mol/L (6mg/dL) and similarly icterus of chest 150mol /L,lower body and, thighs indicates bilirubin 200 mol/L, legs below knees indicates bilirubin value of 250mol/L and hands& feet indicate SBR >250(mol/L) (>15mg/dL).Clinical assessment of bilirubin depends on varying factors like colour perception which is different for different individuals ,the skin pigmentation for different neonates,and the colour and intensity of examining light. Various studies failed to identify a good correlation between clinical assessment and TSB value and clinical assessment sometimes fails to identify clinically significant hyperbilirubinemia(42)(43)(44)**.**

Many studies analysing the utility of clinical evaluation of jaundice for screening have found clinical evaluation to be not reliable. Though there was correlation

between clinical and serum bilirubin estimation, clinical estimation often underestimated significant hyperbilirubinemia thus leading to complications of hyperbilirubinemia. These studies also found that the inter observer variability is unacceptably high.(9)(10)(11).Clinical recognition and assessment of severity of jaundice can be difficult ,which is particularly true for dark skinned people(45).

Serum bilirubin estimation

Serum bilirubin estimation is considered to be the gold standard for evaluating jaundice. The problems associated with serum bilirubin estimation are that it is an invasive procedure and may require multiple sampling and also there is variation in the serum bilirubin value obtained depending on the method of bilirubin estimation.

Hour -specific serum total bilirubin (STB) nomogram of Bhutani et al (12) is widely used to predict the risk of subsequent significant hyperbilirubinemia and also for identifying need for additional evaluation(13). Though, age-specific STB nomogram has performed as well or better than other methods of predicting significant hyperbilirubinemia, it requires an invasive procedure.(46)

Serum bilirubin estimation in the early days were based on biliverdin measurement or on icteric index assessment. But the drawback of icteric index assessment is other serum pigments like haemoglobin, carotenes also contributes to the icteric index limiting its usefulness.(47). In 1883, Ehrlich treated bilirubin in urine with diazo reagent and found that a red blue coloured pigment is formed

and this diazo reaction was adopted for serum bilirubin estimation by van den Bergh in 1918after which it was widely adopted for clinical practise for bilirubin quantification. Van den Bergh and Muller also differentiated direct and indirect bilirubin based on the property whether bilirubin reacted with the diazo reagent without or with the addition of alcohol and this differentiation helps in determining the type of jaundice. There are various methods currently available for biochemical estimation of serum bilirubin.Commonly used biochemical methods are Diazo method,Peroxidase method, Peroxidase Diazo method,High pressure liquid chromatography, Simple colorimetric method for the estimation of plasma biliverdin and Spectrophotometric method.

The drawback of serum bilirubin estimation is that it is an invasive procedure and sometimes may turn painful for the new born inflicting multiple pokes.In addition, a wide range of intra and inter laboratory variability is noticed in the performance of the bilirubin analyser.

Transcutaneous Bilirubin estimation

The basic principle behind transcutaneous bilirubinometer is the high correlation between the serum bilirubin value and the cutaneous bilirubin level .The transcutaneous bilirubinometer works by directing light to the skin of neonate and then measures the intensity of specific wave length returned.

Lights of different wave lengths are directed to the new born skin and the optical signals reflected from the neonates' subcutaneous tissue is analysed. The

photocell in the meter converts optical signals to the electrical signals which is further analysed by a microprocessor which generates the serum bilirubin value from the electrical signal. Different bilirubinometers differ in the number of wave lengths used.

Skin components which interfere with the spectral reflectance commonly in neonates are dermatologic maturity, haemoglobin, melanin and bilirubin

Earlier bilirubinometers used only a few wavelengths and hence the impact of dermal maturity and melanin content was significant and there was no provision to overcome these factors. These made it necessary to have different references for different population and different age groups .Newer bilirubinometers like bilicheck performs a spectral analysis of more than hundred wave lengths and this allows exact deduction bilirubin level without the interference of melanin or maturation of skin.

Compared to the early version of bilirubinometers, the newer versions have several advantages One of the early bilirubinometer to be used was the ColorMate III which used Xenon flash tube and light sensors which measured wave length from 400 -700 nm. The major drawback of this device was the requirement for a baseline TSB reading on each neonate shortly after birth. In recent studies, the newer version of the bilirubinometer JM-103 showed much better correlation than the earlier JM-101 (48)

Measurement principle of JM-103

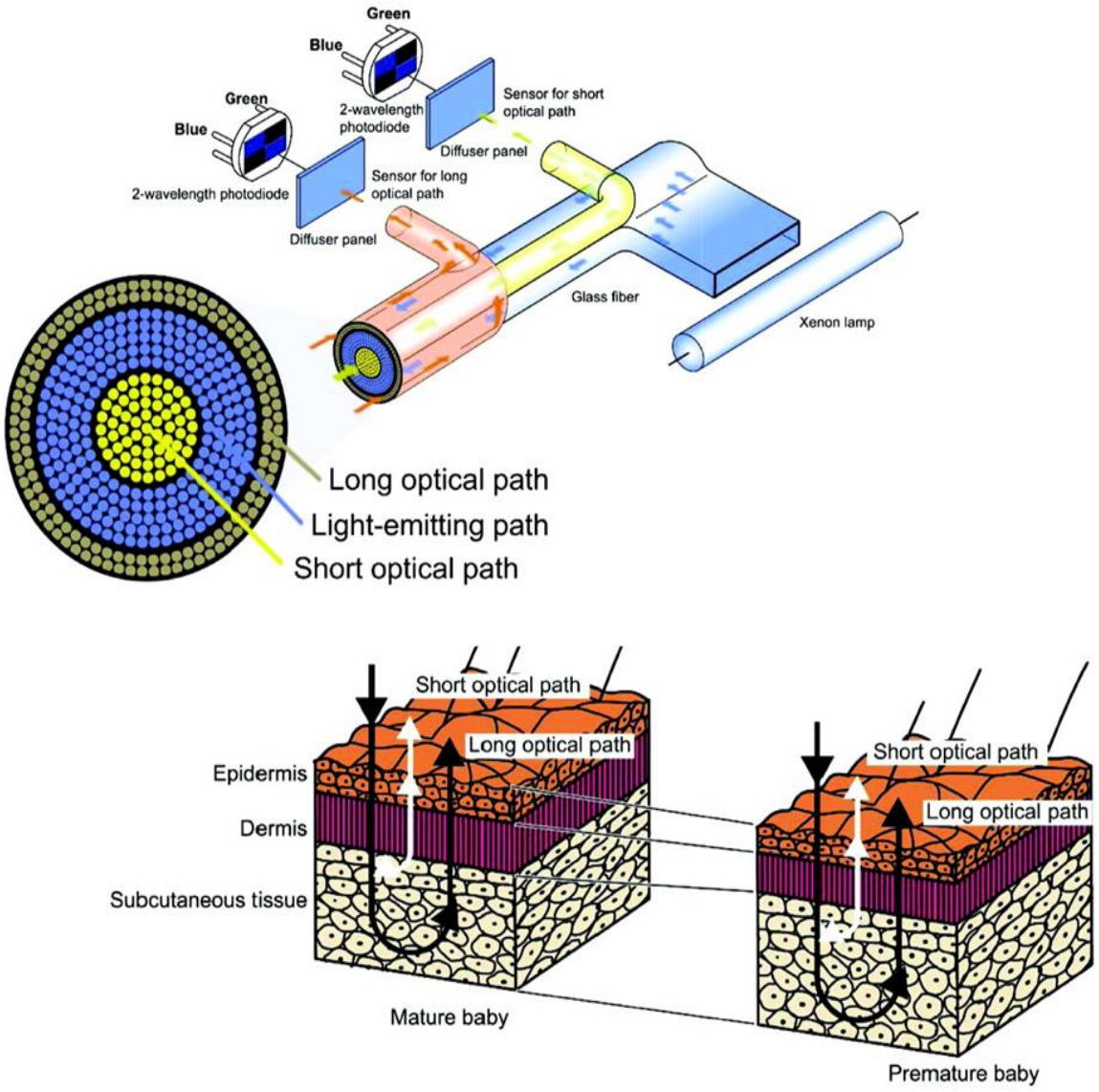
The JM 103 measures the bilirubin of the subcutaneoustissue in new-born by measuring the optical density difference of reflected light at 450 and 550 nm neonates skin. The characteristic feature of JM103 is in this bilirubinometer's measuring probe- two optical paths are incorporated which helps to minimise the interference due to skin maturity or melanin. The reflected light from the subcutaneous tissue passes through two pathways: those reflected from shallow areas of subcutaneous tissue passes through the inner core which is referred as short optical path whereas light reflected from deep areas pass through the long optical axis or the outer core Photo-diodes identifies the reflected light and converts it into electrical activity which is analysed by the microprocessor to estimate the TcB value.

The following pictures (Figure 3& 4) show a JM103 transcutaneous bilirubinometer and the technique of using it to estimate TcB levels in a newborn.

Figure-3


AVG
mg/dL
Dräger
Dräger Service
PMS Date :
22/9/14
Next Due :
21/9/1
JM-103

Figure-4


Green
Blue
2-wavelength photodiode
Sensor for short optical path
Diffuser panel
Green
Blue
2-wavelength photodiode
Sensor for long optical path
Diffuser panel
Glass fiber
Xenon lamp
Long optical path
Light-emitting path
Short optical path
Short optical path
Long optical path
Epidermis
Dermis
Subcutaneous tissue
Mature baby
Short optical path
Long optical path
Premature baby

Transcutaneous bilirubinometer JM 103

BiliCheck is one of the newest bilirubinometers available. It uses reflectance data from multiple wave length reading .The use of multiple wavelength(400 to 760 nm) readings allows correction for differences in skin pigmentation and hemoglobin, eliminating the need for a patient-specific baseline reading.

Comparison of Tcb and TSB

There are several studies in literature to demonstrate the accuracy and reproducibility of transcutaneous bilirubin estimation in estimating serum bilirubin level.

A study published in paediatrics 2000 by Vinod K Bhutani et al hypothesised that TcB measured using Bilicheck device is equivalent to measurement of TSB in a diverse racially different population of term and near term neonates and predicts future development of hyperbilirubinemia.

They evaluated a total of 490 term and near-term new-born who were racially diverse.The evaluation was done using multiple Bilicheckdevices(a total of 11 devices) at 2 separate institutions. All transcutaneous bilirubin evaluations were paired with a heelstick TSB measurement by high performance liquid

chromatography and by diazodichlorophenyldiazoniumtetrafluoroborate technique.

The study showed that the correlation of total serum bilirubin estimation by HPLC to TcB by bilicheck was linear and found to be statistically significant. The study also analysed the inter-device precision and found it to be 0.68..

They concluded that bilirubin estimation by bilicheck device was accurate and reproducible in term and near term new born of diverse ethnic groups. They also advised that infants with pre-discharge bilicheck values above75th percentile of hour specific TSB values on the bilirubin nomogram may be considered to be at high risk for subsequent excessive hyperbilirubinemia(49).

Rubaltelli FF et al conducted a study with the objective of answering the following hypotheses:

1)TcB measured by bilicheck correlates well with TSB as checked by HPLC and standard laboratory methods.

2) gestational age, infant race, body weight or postnatal age interferes with TcB measurement in neonates;

3) the variability of Tcb value measured is comparable with the variability of TSB measured; and

4) Comparability of TcB measured from the fore head and the sternum .

Newborn infants who were>30 weeks' gestational age and <28 days and who underwent tests for TSB as part of their normal care were included in the study .The study was done in 6 different European hospitals and a total 210 infants were included in the study picking 35 babies from each center .Total serum bilirubin was done with paired measuring of TcB values from the fore head and sternum was obtained.TSB levels were determined by the serum bilirubin method in use at each site, and all HPLC-B determinations were made at the same, independent laboratory.

They found that the correlation coefficient between TcB obtained over the forehead and bilirubin obtained by HPLC was 0.89. The correlation coefficient between TcB obtained over the sternum and HPLC bilirubin was 0.881.Forehead TcB value slightly overestimated bilirubin in comparison with HPLC. Analysis of covariance demonstrated that bilicheck accuracy was independent of race, birth weight, gestational age, and postnatal age of the newborn.

They concluded that as correlation coefficient for HPLC and TcB value over the fore head is very similar to that found for HPLC and standard laboratory serum bilirubin estimation, hence bilicheck could be used as a reliable substitute of total serum bilirubin estimation .They also found that higher level of serum bilirubin level bilicheck performance was slightly better as compared to standard laboratory methods of bilirubin estimation (50).

Another study published in paediatrics in 2004 by M. Jeffrey Maisels et al looked into the reliability of transcutaneous bilirubin estimation by using JM 103

Jaundice meter. A total of 849 newborns> or =35 weeks of gestation from various racial backgrounds were included in the study .These infants had total serum bilirubin (TSB) levels measured on clinical indication, and transcutaneous bilirubin (TcB) levels were obtained within 1 hour of the TSB levels. They concluded that measurement of TcBby JM-103 jaundice meter has good correlation with TSB values except in black infants ,where the TcB tends to overestimate serum bilirubin value hence dangerously high bilirubin level will not be overlooked(48).

Mussavi M et al studied the correlation coefficient between the capillary, transcutaneous and the serum bilirubin estimation by laboratory method. More than 400 babies were recruited and they found good correlation between all the three methods .The authors concluded that as there is only very low difference between JM103 and capillary methods, these two methods could alternatively be used instead of usual laboratory method.(51).

Effect of site on the quality of TcB results

The body site used to check TcBvalue has been shown to have an effect on the accuracy of the results. The measurements made on the sternum and forehead showed the best correlation with TSB.

Ebbesen F et al compared the correlation of TcB measured at the fore head, sternum. , knee and the foot with TSB and found that the forehead and sternum TcB correlated well with TSB and measurements on the knee and foot showed

unacceptable correlation. The total number of babies recruited for the study was 488. They also found that in NICU babies, TcB measured on the fore head showed a better correlation than sternal TcB which is statistically significant(52).

Randeberg et al in their study found that TcB measurements on neonates taken from the back, heel, or thigh did not correlate as well with TSB as those taken from the forehead (53)

Maisels et al. found better correlation with TSB when TcB was obtained on the sternum (r = 0.953) when compared with the forehead (r = 0.914).They also suggested that measurements be taken from the sternum, which is less likely to be exposed to sunlight or ambient light, may be more desirable, especially when measurements are taken after infants have been discharged from the hospital(48).

Trikalinos TAet al did Systematic review of the effectiveness of the specific screening modalities in decreasing the incidence of bilirubin encephalopathy..

They concluded that effects of screening on decreasing bilirubin encephalopathy is unknown, although screening can predict hyperbilirubinemia and no robust evidence to suggest that screening is associated with favourable clinical outcomes(54).

Accuracy of Serum Bilirubin testing and TcB measurement

In most studies comparing TcB measurement with TSB measurement, TSB was measured using diazo-based methods (55) which has interferences with haemoglobin and intracellular compounds (56).Another problem commonly encountered in newborn is that the blood collected from them is often haemolysed which will affect the accuracy of clinical laboratory method. The precision and accuracy of TcB as compared to HPLC method which unlike the routine laboratory method is not influenced by the interference from lipemia or haemolysis. Recent practise guidelines by National Academy of Clinical Bio-chemistry laboratory medicine concluded that TcB measurement by Bilicheck and JM103 provides results comparable to Total serum bilirubin value(57).

Clinical implication of bilirubin estimation

Two clinical implications of non-invasive bilirubin estimation are impact of TcB measurement in determining significant hyperbilirubinemia and the actual reduction of invasive bilirubin estimation.

L Briscoe et al conducted a study to evaluate the accuracy of TcB measurement in determining the need for serum bilirubin measurement in full term babies and found a good correlation between SBR and TcBmeasurement.They found that a TcB value of more than18 mg/dl detected clinically significant jaundice with a sensitivity of 100% and specificity of 45% and if the blood samples had only

been taken from babies with a TcB greater than 18mg%,the number of samples taken would have been reduced to 34%(58).

A reduction of 80% in blood sampling was noticed after the introduction of TcB measurement by Ebbesen and associates and the authors recommended to use a TcB limit which is 70% of the currently recommended TSB limits for phototherapy, to decide whether TSB needs to be measured.(59)

Petersen JR et al did the study to analyse the decrease in readmission rate for hyperbilirubinemia after implementing the policy of transcutaneous bilirubin testing in hospital. They retrospectively analysed the total number of births, newborn readmission rates because of hyperbilirubinemia, the number of bilirubin measured and the length of staying two epochs before and after the implementation of transcutaneous bilirubin testing policy.

They concluded that access to TcB testing reduces hospital readmission rate for hyperbilirubinemia.(60)

Limitation of TcB

Though most studies shows a good correlation between TcB estimation and serum bilirubin estimation, there are exceptions.

An Indian study by RakeshLodha et al at the All India Institute of Medical Science compared estimation of total serum bilirubin by bilicheck a multi wave spectral refractancebilirubinometer with laboratory serum bilirubin

estimation.They compared 121 paired bilirubin estimation in term babies who appeared clinically icteric more than 8 mg/dl.

The study found that there was a poor correlation betweenTcB estimation and also found that the agreement between TSB and TcB was poor in the subgroup where the TSB was more than 13 mg/dl. Similar results were reported earlier using a different transcutaneous bilirubinometer. The sensitivity of clinical judgement for values >13 mg/dl was poor, though the specificity was good. It seems that the TcB estimation reconfirms the clinical judgement specially for higher bilirubin levels in pathological range (>13 mg/dl)(61).

Tcb value measurement using TcB devise can be affected by a variety of factors like exposure to sunlight and phototherapy(62)(63)(64). The other factors influencing total serum bilirubin estimation are haemoglobin concentration ,the melanin content of the skin and the dermal thickness .This has led most facilities to limit the use of TcB to infants less than 10 days old but there are certain studies showing the reliability of TcB in adult population. Care must also be taken to avoid testing skin that is bruised, has a birthmark, or is covered with hair. As phototherapy bleaches the skin, both visual assessments of jaundice and TcB measurements in infants undergoing phototherapy are not reliable.

Bilirubinnomogram

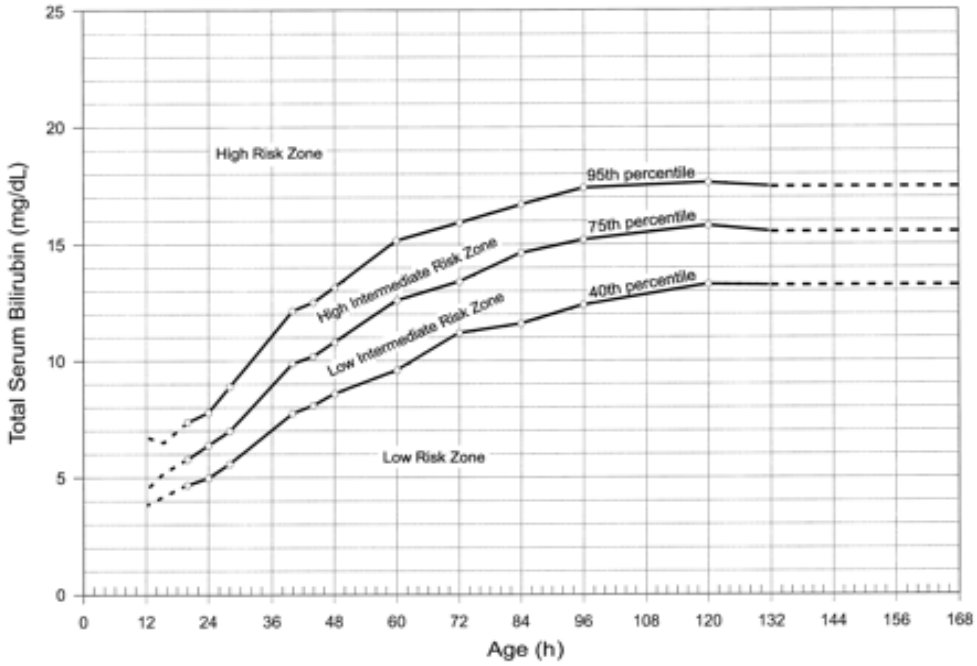
The concept of hour specific bilirubin nomogram was first introduced by Bhutani et al and the hour -specific serum total bilirubin (STB) nomogram of Bhutani et al is widely used and accepted to predict the risk of subsequent significant hyperbilirubinemia and also for identifying need for additional evaluation (Figure 5).

Vinod K. Bhutani et al in their study tried to analyse the predictive ability of universally measuring pre-discharge serum bilirubin level to assess the risk of subsequent significant hyperbilirubinemia in healthy term and near-term newborn who are direct Coombs negative.

A total of 13003 healthy direct Coombs negative term and near-term newborns were included in the studyThey constructed a percentile-based bilirubin nomogram for the first week of life. They also assessed the accuracy of the pre-discharge TSB for the predictor of subsequent degree of hyperbilirubinemia.

In their study, they found that 6 % of the babies were in the high risk zone of which around 40% remained in the high risk zone. Around 32 % babies were in the intermediate risk zone from which 6.4% the post discharge TSB moved to the high risk zone from the upper intermediate zone and 0.48% from the lower intermediate zone. 61.8% of babies were in the low risk zone and there was no measurable risk for hyperbilirubinemia.

Figure-5



They concluded that an hour-specific TSB before hospital discharge is useful

in predicting which newborn is at low, intermediate and high risk for developing clinically significant hyperbilirubinemia. High risk is defined as TSB value more than 95th percentile for age in hours. They also concluded that measuring TSB as a universal policy will help to facilitate targeted intervention and follow up in a safe, cost effective manner(65).

The usefulness of such a data is widely accepted and AAP has stated that 'the best documented method for assessing the risk of subsequent hyperbilirubinemia is to measure TSB or TcB and plot the results on a nomogram' (66).When evaluating the risk of hyperbilirubinemia using TcB meter, nomograms based on TSB may not be appropriate Availability of adequate nomograms is therefore

mandatory to correctly perform the evaluation in neonates of various genetic background or with different transcutaneous bilirubinometry techniques

Giovanna Bertini et al prepared transcutaneous bilirubin nomogram to establish a normative data .They performed BiliCheck measurements

on 175 term Italian new-borns after excluding the babies who are at high risk of hyperbilirubinemia like ABO incompatibility ,Bruising and those neonates requiring phototherapy. They did the first bilirubin evaluation at 24 hours and then repeated at 24 hours interval till 5 days of life and separate nomogram forthree gestational age groups 37-38 weeks 39- 40 weeks and 41 weeks were constructed plotting the 5th, 50th and 95th percentiles(67).

The drawback of the study was that population baseline data, description of statistical analysis, enrolment and exclusion criteria were not provided and this nomogram described the natural course of hyperbilirubinemia by days instead of hours of life, as actually recommended by the AAP. The nomogram was based on bilirubin level done on.daily basis as opposed to hourly basis as suggested by AAP

Maisels and Kring published a nomogram based on 3984 healthy North Americans neonates with gestational age more than 35 weeks till 96 hours of life.

They recruited a total of 3984 infants and obtained 9397 TcB measurements. Around 17 % of the babies were late preterm. Around 40 % of babies were born by LSCS and 67% of the babies were on exclusive breast feeds.

They used the Draeger Air-Shields JM-103 transcutaneous jaundice meter.They found that the rise in TcB level was in a linear manner and maximum rise is observed at 6 to 18 hours and then less rapid rise observed from 18 to 42 hours and then a much slower increase until peak levels occurred and peaked by 96 hours of life.

Their conclusion was that any baby whose bilirubin levels were more than 95th percentile, or a rapid rise of more than 0.22 mg/dL per hour in the first 24 hours of life , 0.15 mg/dL per hour in the next 24 hours and after which a rise of more than 0.06 mg/dL per hour requires closer evaluation and monitoring(68)

Another study by Sanpavat et al aimed at developing an hour-specific nomogram, using transcutaneous bilirubin values determined using Bilicheck in Thai newborninfants.They also assessed the risk zones to predict the future development of hyperbilirubinemia.

A total of 392 babies were included in the study of which 108 babies were excluded from the nomogram development due to requirement of phototherapy and hemolytic diseases. For constructing the risk zone assessment, all the 392 babies were included.

They concluded that a TcB of more than 90th percentile identified risk of subsequent hyperbilirubinemia with diagnostic sensitivity, specificity, positive predictive values and negative predictive values of 96.9%, 78.8%, 29.1%, and 99%.any bilirubin value below 10th percentile is considered as very low risk zone 10th to 25th percentile low risk zone, 25th to 90th percentile as intermediate zone with 25th to 50th percentile being low intermediate and 50th to 90th percentile as high intermediate.(69)

De Luca et al aimed at providing data about skin bilirubin level estimation using bilicheck during the natural course of hyperbilirubinemia.The study was conducted in healthy European neonates with gestational age more than or equal to 35 weeks upto 96 hours of life.

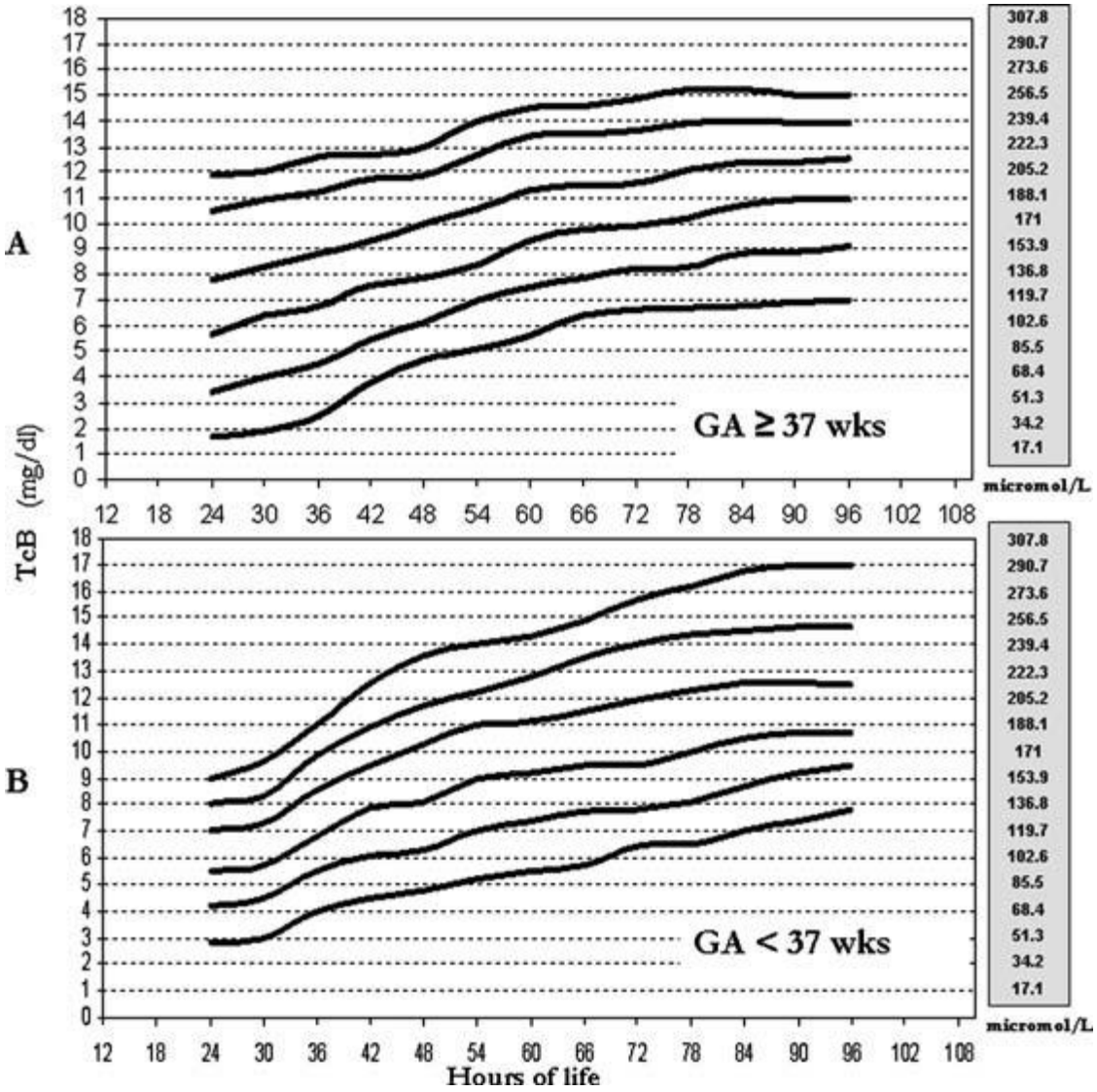
A total of 2198 neonates ≥ 35 weeks were recruited for the study and 35 and 36 weeks babies constitute 26.7% (558).Around 67of babies were on breast feeds and 40 % of the study babies were born by LSCS

All transcutaneous measurements were done with a multiwavelength transcutaneous bilirubinometer (RespironicsBiliCheckTM).

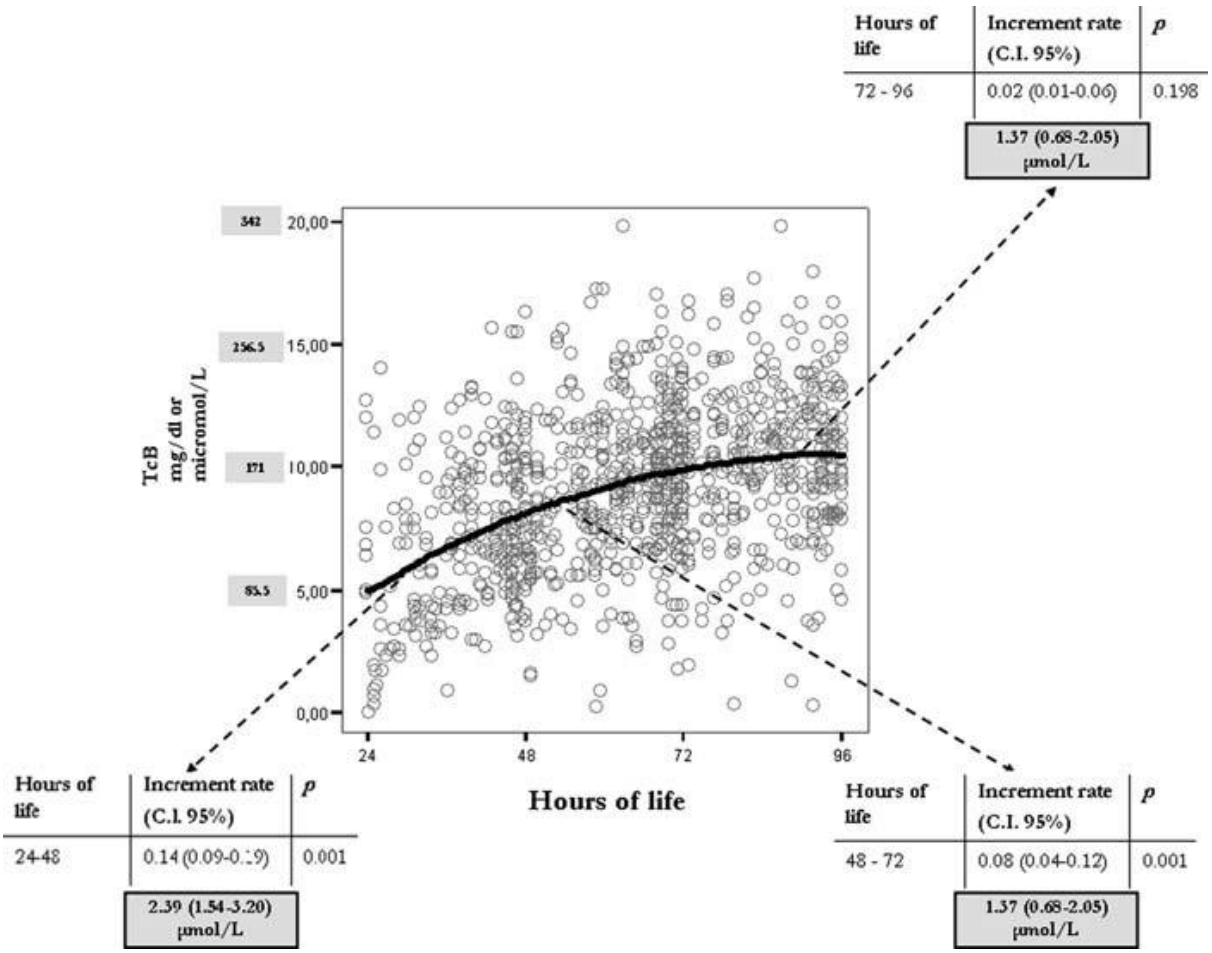
The TcB value obtained was utilised to draw 10th, 25th, 50th, 75th and 95th percentiles nomogram for of skin bilirubin, both for term and nearterm babies (Figure-6). They also noticed a rapid rise of bilirubin in the first 48 hours(0.14mg/dl/hour)followed by a less rapid rise in the next 24 hours L (0.08

mg/dL/per hour) and a minimal rise thereafter(<0.04 mg/dL/per hour)(70) (Figure-7).

Nomograms showing 10th, 25th, 50th, 75th, 90th and 95th percentiles for TcB measured in term (A) and near term babies (B) (Figure -6)



Mean TcB rate of increase (expressed in mg/dL/h) and linear regression data for different hours of life.(Figure-7)



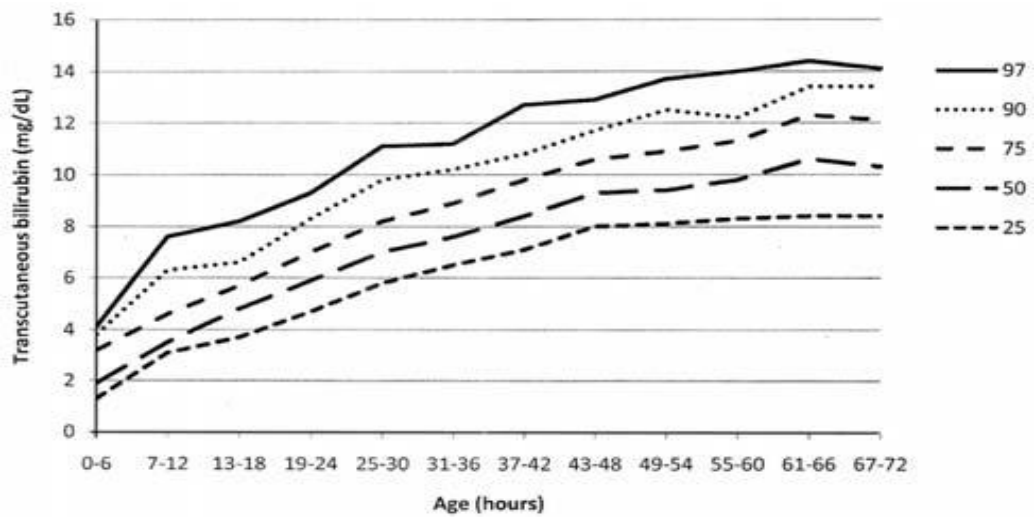
SathishMisra et al aimed at providing normative data for transcutaneous bilirubin levels for babies≥ 35 weeks. They constructed nomogram for first 72 hours of life using a multiwavelength reflectance transcutaneous bilirubinometer-Bilicheck. They performed 925 TcB measurements on 625 healthy newborn infants till 72 hours of life of which 35 and 36 weeks babies constituted only 10%.Most of the babies were breast fed though the exact percentage has not been described.

Age-specific percentiles values for each 6 hour period starting at 0 hour of age were calculated and with this value, an age-specific TcB nomogram was developed using different percentile values (Figure -8). After constructing nomogram, diagnostic ability predicting hyperbilirubinemia (requirement of phototherapy) of each percentile curve was calculated.

They found that the TcB value rises in a linear fashion and maximum rise is observed in the first 24 hours of life (Table-1). The 50th percentile curve of age-specific TcB nomogram had high negative predictive value (99.8%) and acceptable positive predictive value (16.4%) for prediction of hyperbilirubinemia.

Their study included both term and late preterm infants and they pointed out that the need for phototherapy in late-preterm neonates was significantly higher as compared to term neonates Nearly 90% of neonates enrolled in the study were term.It is likely that with increasing proportion of late-preterm neonates, predictive ability of nomogram would change(71).

Age-specific Nomogram (Figure – 8)



Rate of Rise in TcB Levels in Various Percentiles at Different Ages (Table - 1)

Percentile	**Increase in TcB Level, mg/dl per h**		
	6–24 h	**24–48 h**	**48 – 72 h**
25th	0.19	0.13	0.02
50th	0.22	0.14	0.04
75th	0.22	0.14	0.06
90th	0.25	0.15	0.07
97th	0.29	0.16	0.07

Cost-Effectiveness of TcB Measurements

Currently, no studies have been published to determine the costs associated with the use of TcB measurements in clinical practice. A number of studies have suggested that the increased cost of TcB measurements is offset by a decreased requirement for serum bilirubin measurements (72) (73)(50). Similarly, Petersen et al. (60) attempted to evaluate the costs associated with TcB by estimating the impact of TcB measurements on hospital charges. Although data about actual costs was not reported, they found that there were decreased charges as a result of fewer readmissions of newborns because of hyperbilirubinemia. However, the decrease in readmissions was offset by increased charges associated with TcB measurements and increased number of newborns treated by phototherapy. The net result was a small but statistically insignificant increase in charges after the introduction of TcB measurements.

Rationale for the study

The lack of transcutaneous bilirubin nomogram exclusively for late preterm infants, who are more prone for hyperbilirubinemia was the main factor behind this study. This nomogram will provide the basic data regarding the natural rise of bilirubin in this specific mainly breast fed population.

This hour specific nomogram may be used to assess the risk of laterdevelopment of significant hyperbilirubinemia aftervalidating the nomogram.Thismay help to circumvent theinvasiveness of serum bilirubin estimation.

MATERIALS AND METHODS

Study design

Prospective observational study.

Setting

The study was conducted in the Neonatal nurseries and postnatal wards of CMC Vellore. The study was done over a period of 1 year (February 2014- January 2015).Christian Medical College. Vellore is a tertiary care teaching centre in south India.

Participants

All babies born between 34 weeks to 36 weeks + 6 days (Late Preterm) delivered in Christian Medical College were included in the study.

Inclusion Criteria:

1.All late preterm babies born in Christian Medical College Vellore.

Exclusion Criteria:

1. Rh isoimmunisation, ABO incompatibility
2. Major congenital malformation
3. Feeds not initiated within 48 hours of birth.
4. Lack of parental consent

Intervention in babies meeting inclusion criteria

Transcutaneous bilirubin was estimated at regular intervals till 120 hours or till discharge. Evaluation was stopped if baby was started on phototherapy before 120 hours.

Informed Consent

Informed consent was taken from the parent if the baby satisfied the inclusion criteria.

Ethics clearance

The study was cleared by the Institutional Review Board and Ethics committee.

Method details

Detailed Research plan:

The study was an observational cohort study. Late Preterm babies who fit into the study criteria were identified and parents approached for informed consent.

A profomawas maintained which contained the basic information of the mother and the baby along with any predisposing factors for the development of hyperbilirubinemia.This also contained the feeding history of the baby. Transcutaneous bilirubin measurement was done at 6 hours intervals in the first 24 hours of life (6,12,18 and 24 hours) and then 12th hourly till 120 hours or till discharge of the baby . For all time frames, bilirubin was done at hour ± 2 hours.

If babies were commenced on phototherapy, only pre- phototherapy treatment values were considered. All babies who were evaluated for jaundice as per unit policy were screened for pathological causes of jaundice. If this revealed the presence of haemolytic hyperbilirubinemia, baby was excluded from the study . Similarly, any condition likely to cause cholestatic jaundice (sepsis, intrauterine infections) was excluded. The decision to start phototherapy was according to the unit protocol and those babies requiring exchange transfusion were excluded from the study.

Hour specific trancutaneous bilirubin nomogram was constructed in the 5^{th} 10^{th} 25^{th} 50^{th} 75^{th} 90^{th} and 95^{th} percentile. As part of secondary outcome, those babies whose serum bilirubin was estimated as part of unit policy (for clinical jaundice) had a corresponding TcB estimated and the correlation between these values was estimated.

Sample size

The sample size was calculated as follows: For every time frame, we calculated the minimum number of observations needed for achieving various degrees of precision with 95% confidence levels. The table is given below (Table -2).

Standard Deviation	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5
Absolute Precision	2.5	2	1.75	1.5	1.25	1	.9	.8
Desired confidence level (%)	95	95	95	95	95	95	95	95
Required sample size	19	29	38	52	74	116	143	182

Considering the number of late preterm deliveries, we opted for absolute precision of 0.9 with 95% confidence interval and the sample size was found to be 143 – 150 TcB values in each time period.

Statistical methods:

Transcutaneous bilirubin levels would be obtained for designated times (6^{th} hourly till 24 hours and then 12^{th} hourly till 10 hours of life) and 5th, 10th, 25th, 50th,75th,90th,95^{th}percentilesTcB values will be obtained and the nomogram will be plotted.

Data Analyses:

Statistical methods to be used for the primary outcome;

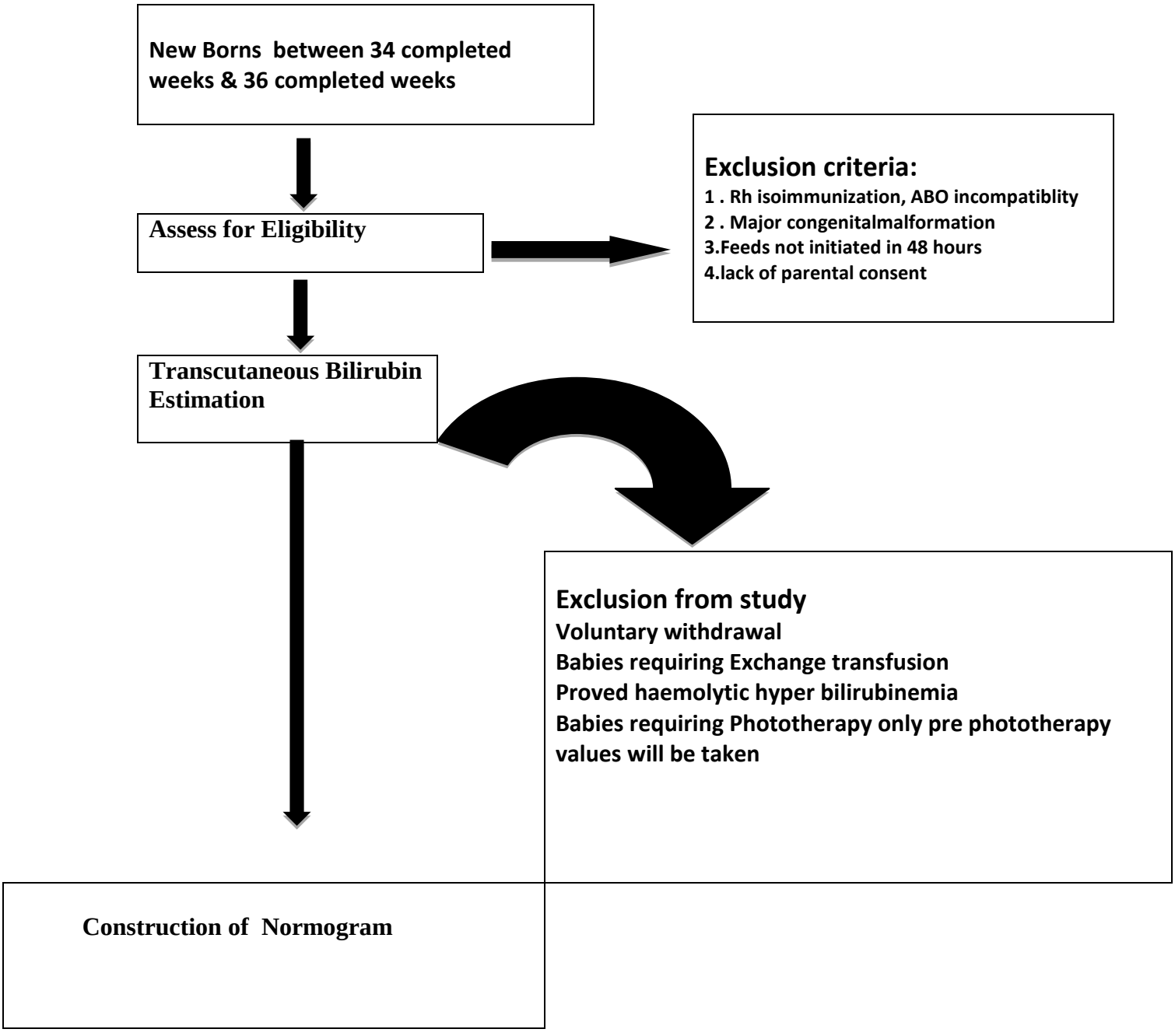
Primary outcome was the construction of hour- specific nomogram.

Rate of rise of bilirubin in specific time interval would be calculated for each centile and mean rise of bilirubin in each time epoch would be calculated.

Correlation and the difference between the serum bilirubin and the Transcutaneous bilirubin would be quantified. Level of agreement would be analysed using Bland Altman plot.

Comparison of means between the TcB observations of the different sexes would be done using independent T-test and between the different gestational ages (if possible) using one way Anova test. Significance was defined as a p value <0.05.

Transcutaneous bilirubin nomogram in late preterm for prediction of Significant hyperbilirubinemia (Figure-9).



RESULTS

During the study period from February 2014- January 2015, 270 babies satisfying the inclusion criteria were recruited in the study. The graph below gives the course of the study. A total 270 babies were recruited for the study to obtain a minimum of 143TcBvalues in each epoch. About 50 % of babies could not be followed upto 120 hours of life because of variable reasons- major causes being starting of phototherapy for hyperbilirubinemia as per the unit protocol and early discharge before the completion of 120 hours.

Figure - 10

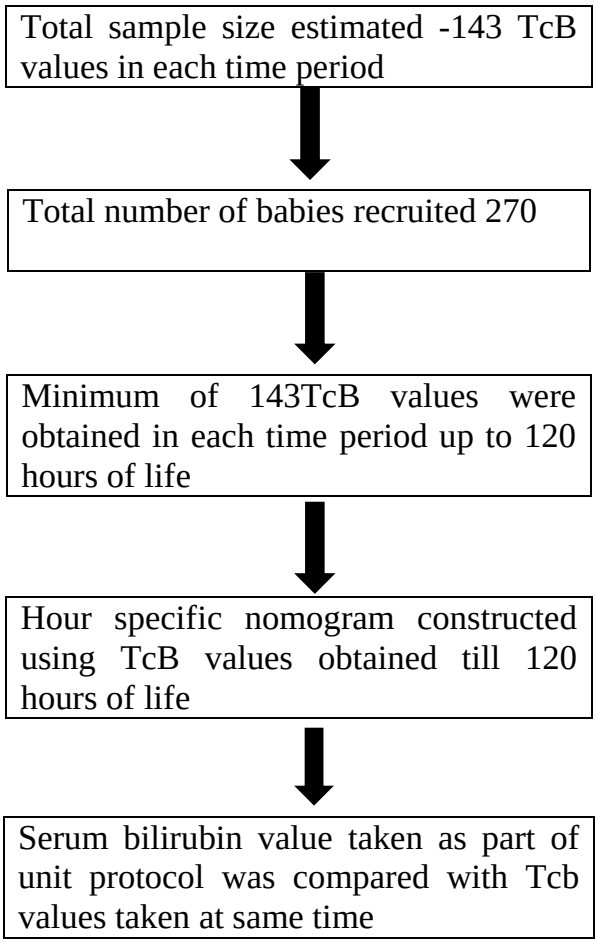


TABLE 3 DEMOGRAPHIC VARIABLES.

Gestational age – Mean (Standard deviation)	35.6 weeks (.819)
Weight –Mean (Standard deviation) Range	2274.12 grams (411.946 grams) 1140 – 3500g
SexBoys	140 - 51.8 %
Girls	130 -48.2 %
Feeding Exclusive Breast feeding	155 -57.4%
Breast feeding with artificial feeds	115 -42.6 %
Mode of delivery vaginal Delivery	138 -51 %
LSCS	132 -49 %

As shown in table 3 the mean gestational age of babies recruited was 35.6 weeks with a standard deviation of 0.8 weeks and the mean birth weight was more than 2200 grams with a standard deviation of 411 grams.Babies with awide range of birth weight wererecruited to the study and the birth weight ranged from 1140g to 3500g.

There was almost equal distribution of boys and girls in the study.Only around 57 % of babies were on exclusive breast feeding the other 47% being on supplementary feeds. Supplementary feeds were banked breastmilk or diluted cow's milk. The indication for supplementary feeds was mainly due to non-

availability of mother in the first 48 hours or lack of breastmilk.Those babies not started on feeds by 48 hours of life was not included in the study.

There was also almost equal distribution of babies born by vaginal delivery and by CS.

TABLE 4 GESTATIONAL AGE DISTRIBUTION

Gestational age	Number of babies	
34 - 34 weeks 6 days	55	20.3 %
35 - 35 weeks 6 days	75	27.8 %
36 - 36 weeks 6 days	140	51.9 %

As shown in Table 4, about 20.3 % of the babies recruited for the study were 34 weeks, 27.8% was 35 weeks gestational age and majority of the babies (51.9%) were 36 weeks gestational age.

TABLE 5 WEIGHT FOR GA DISTRIBUTION

Small for gestational age(SGA)	Number of babies	Percentage
	65	24 %
Appropriate for gestational age(AGA)	200	74 %
Large for gestational age(LGA)	5	2 %

As shown intable 5 majority of the babies were appropriate for gestational age .Of the total 270 babies recruited, 200 babies (74%)were AGA; only 65 babies (24%) were SGA. The proportion of LGA babies was found to be almost negligible (2%).

TABLE 6 DETAILS OF TCB MEASUREMENTS TAKEN DURING THE STUDY PERIOD.

Total number of babies recruited for the study	270			
Total TcB value obtained	N = 2109			
TcB Value	No. of Values	34 weeks	35 weeks	36 weeks
6 hours of life	251	50	71	130
12hours of life	252	52	68	132
18hours of life	248	51	68	129
24hours of life	247	51	68	128
36 hours of life	241	49	68	124
48hours of life	247	50	69	128
60 hours of life	207	38	58	111
72 hours of life	206	40	56	110
84 hours of life	188	36	51	101
96 hours of life	172	30	49	93
108 hours of life	135	29	40	66
120 hours of life	131	28	38	65

Table 6 shows that a total of 270 babies were recruited for the study and the total number of TcB measured over time was 2109 .There was a fairly proportional representation for TcB measurements between the various gestational ages in each time epoch.. As can be seen, we could not achieve sample size (143 measurements) at 108 and 120 hours.

.**Transcutaneous bilirubin nomograms**

Figures 11, 12 and 13 show the transcutaneous bilirubin nomograms for the entire cohort as well as smoothened curves upto 120 hours separately for boys and girls.

FIGURE 11 TRANSCUTANEOUS NOMOGRAM FOR LATE PRETERM TILL 120 HOURS OF LIFE

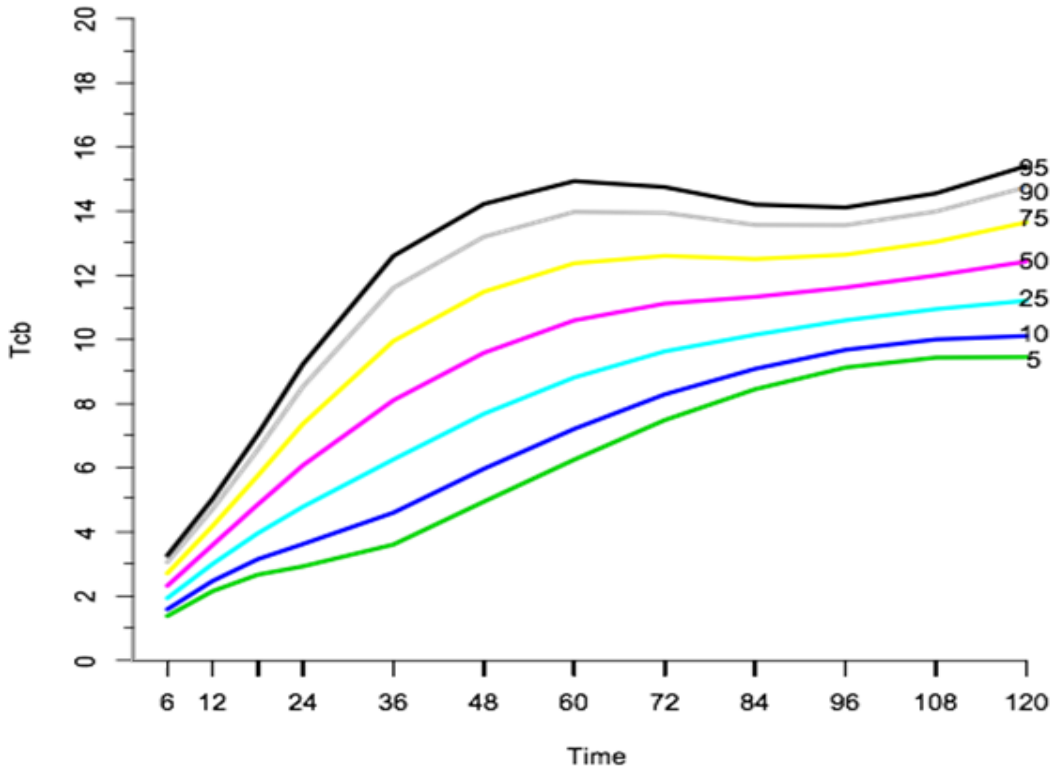


Figure 11 shows the normative data of late preterm till 120 hours of life. The 5th 10th 25th 50th 75th 90th and 95th percentile nomograms were constructed from the data's available. The chart shows a marked rise inthe first 36 hours followed by

a gradual rise of bilirubin till 72-84 hours of life after which the bilirubin rise is negligible.

FIGURE 12 TRANSCUTANEOUS NOMOGRAM FOR FOR LATE PRETERM BOYS TILL 120 HOURS OF LIFE

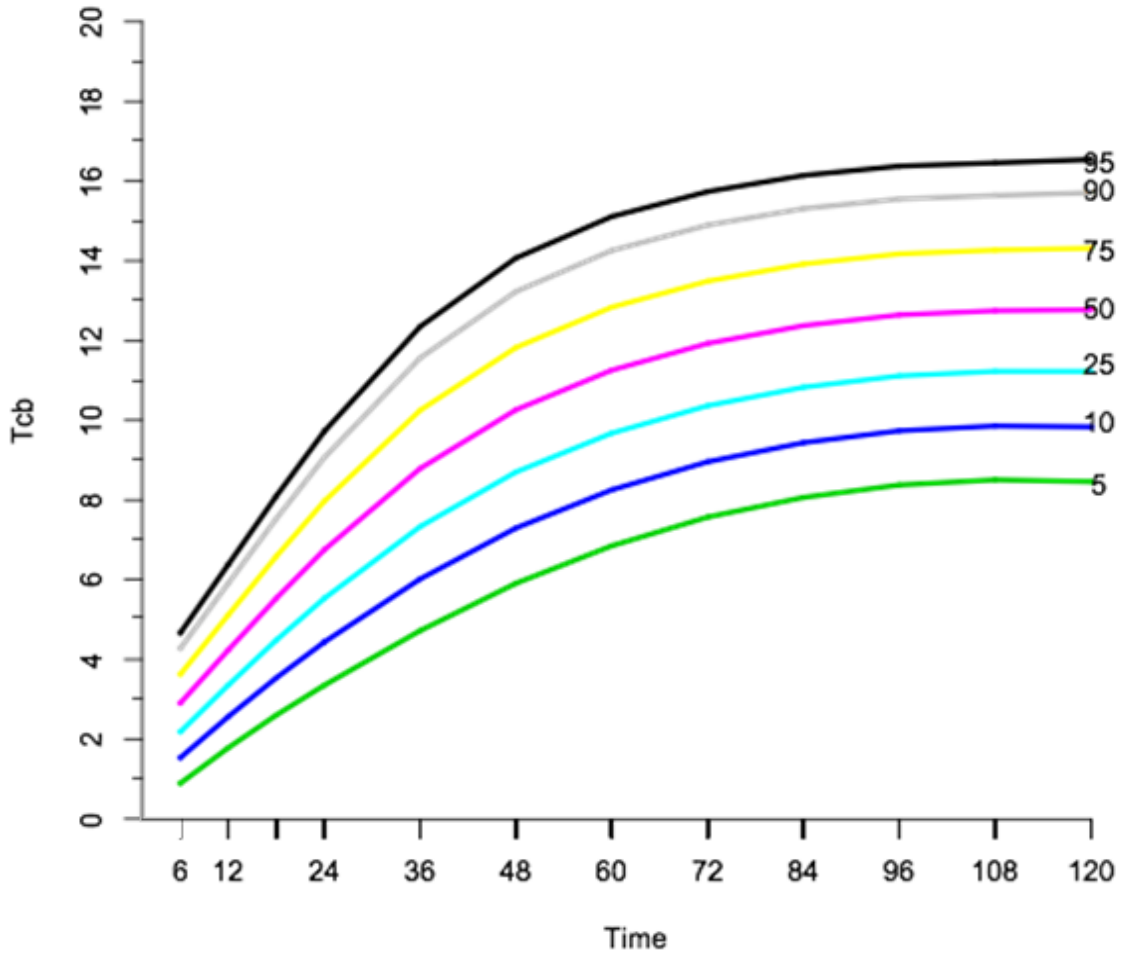


Figure 2 showing the normative data of boys included in the study over a period of 120 hours. A total of 140 boys were recruited in the study .The maximum rise

of bilirubin is noted in the first 24 to 36 hours then a gradual increase in bilirubin noted till 72 to 84 hours of life after which it serum bilirubin rise is negligible.

FIGURE 13 TRANSCUTANEOUS NOMOGRAM FOR FOR LATE PRETERM GIRLS TILL 120 HOURS OF LIFE

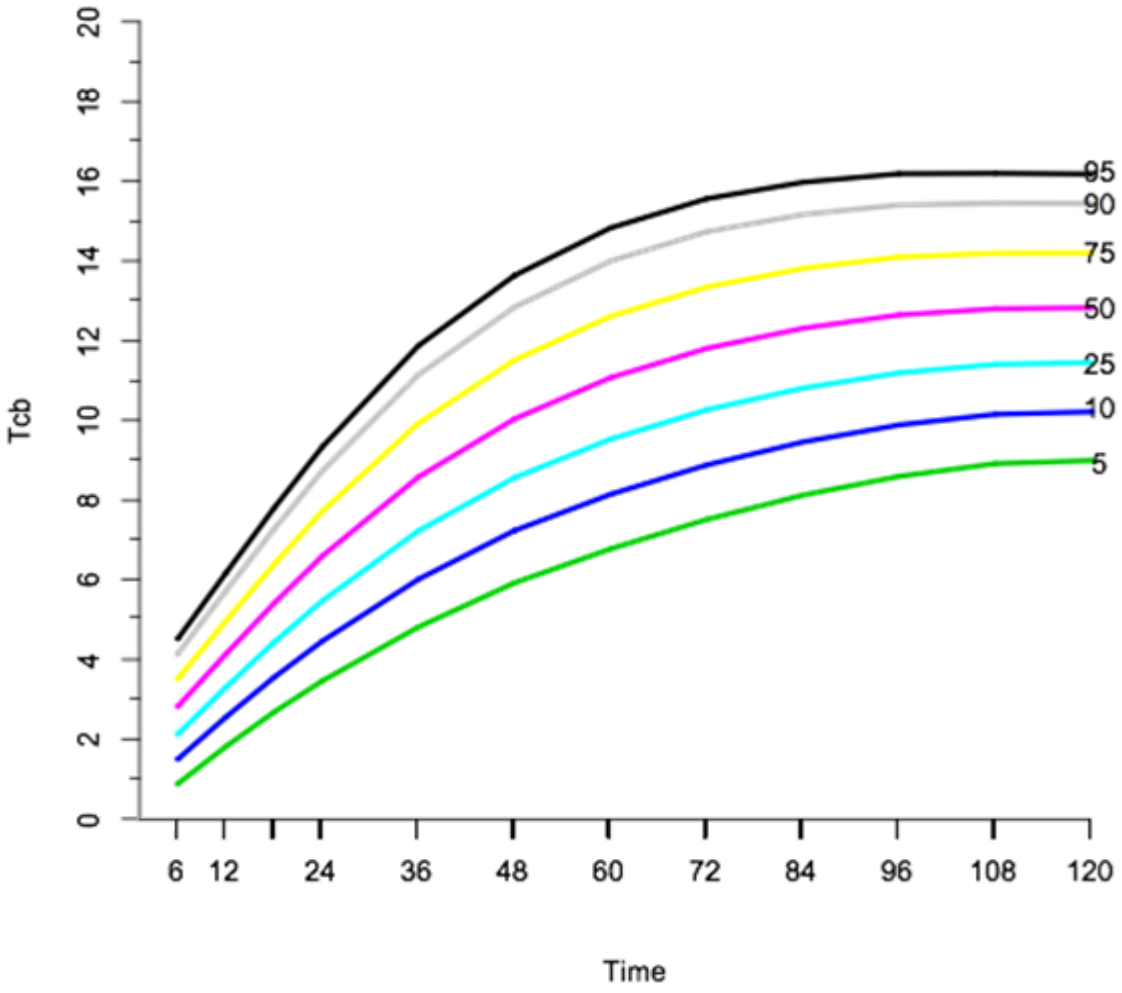


Figure 3 showing the normative data of girls included in the study over a period of 120 hours. A total of 130 girls were recruited in the study .The maximum rise of bilirubin is noted in the first 24 to 36 hours then a gradual increase in bilirubin noted till 72 to 84 hours of life after which serum bilirubin level remains stable

TABLE 7 COMPARISON OF TCB VALUE OF BOYS AND GIRLS AT DIFFERENT TIME PERIODS

Hours of life	Boys		Girls		P value
	Mean TcB Value	Standard deviation	Mean TcB Value	Standard deviation	
6 hours	2.86	0.95	2.82	0.92	0.98
12 hours	4.2	1.41	4.18	1.35	0.47
18 hours	5.54	1.49	5.51	1.39	0.47
24 hours	6.89	1.98	6.74	1.77	0.21
36 hours	8.92	2.18	8.70	2.06	0.355
48 hours	10.32	2.27	10.1	2.06	0.16
60 hours	11.17	2.36	11.05	2.38	0.50
72 hours	11.88	2.26	11.89	2.28	0.925
84 hours	12.29	2.3	12.22	2.15	0.23
96 hours	12.8	2.35	12.79	2.32	0.7
108 hours	12.96	2.09	12.96	1.79	0.86
120 hours	12.67	2.38	12.68	2.16	0.52

Table 7 shows the comparison of mean TcB value in different time epochs of boys and girls along with the P value. At all time periods, there was no significant difference in the TcB values between boys and girls ($p < 0.05$).

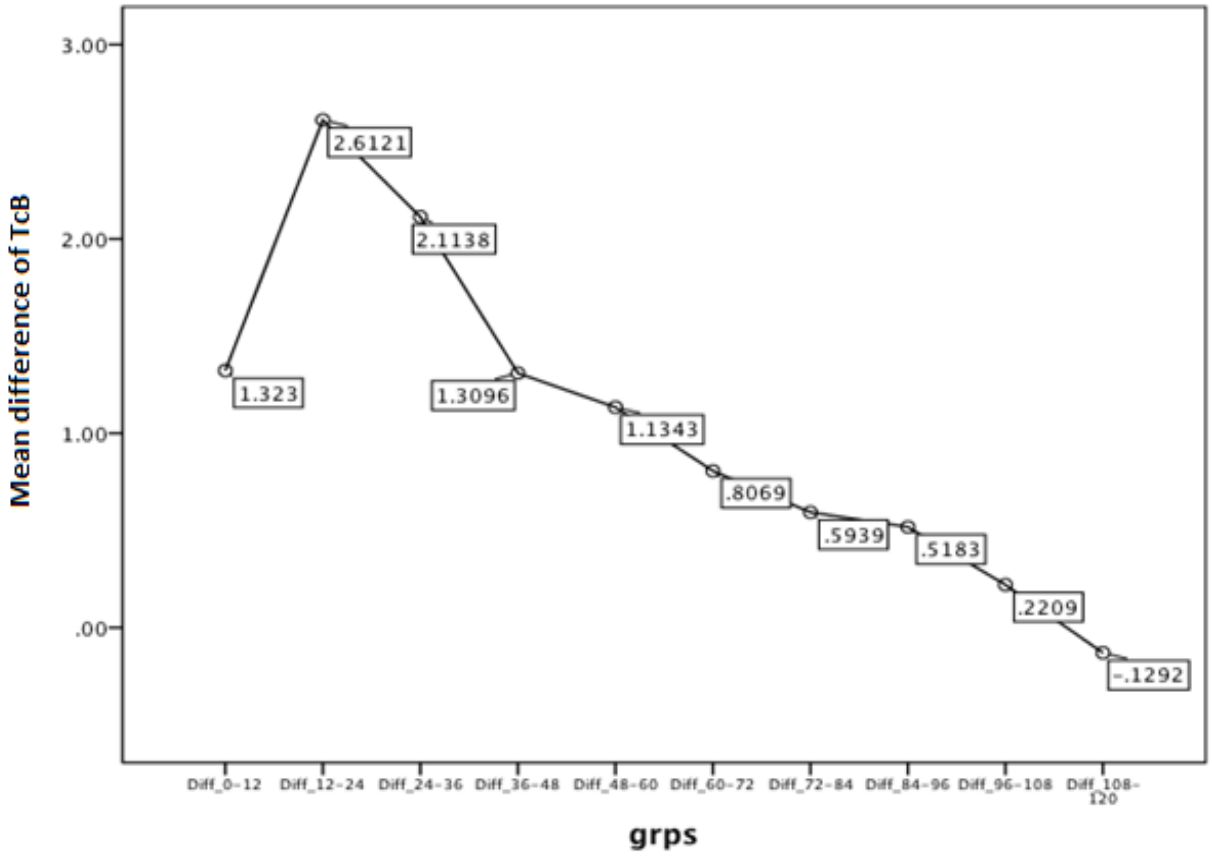
TABLE 8 RISE OF BILIRUBIN IN DIFFERENT TIME PERIOD.

		Rise of TcB in different time epochs					
		6 -12 hours	12- 24 hours	24-36 hours	36-48 hours	48-60 hours	60-72 hours
Total number of babies assessed		243	240	232	228	201	189
Mean rise of bilirubin		1.3230	2.6121	2.1138	1.3096	1.1343	.8069
Percentiles	5	.2000	.9050	.3000	.1450	-.2000	-.7000
	10	.3000	1.4000	.9000	.4000	.2000	-.2000
	25	.7000	2.1000	1.3000	.9000	.6000	.3000
	50	1.3000	2.6000	1.8000	1.3000	1.2000	.7000
	75	1.8000	3.1000	2.6000	1.8000	1.6000	1.2000
	90	2.5000	4.0900	4.0000	2.4000	2.0000	2.0000
	95	2.6000	4.6000	5.0350	2.6000	3.3400	2.6500

		Rise of bilirubin in each epochs			
		72-84 hours	84-96 hours	96-108 hours	108-120 hours
Total number of babies assessed		180	169	134	130
Mean rise of bilirubin		.5939	.5183	.2209	-.1292
Percentiles	5	-.8000	-.9000	-1.3250	-1.7000
	10	-.4000	-.4000	-.9500	-1.4000
	25	.2250	.1000	-.4000	-.7250
	50	.6000	.4000	.2000	-.2000
	75	1.0000	.9000	.7000	.5000
	90	1.4000	1.7000	1.6500	1.2000
	95	1.8000	2.0000	2.2500	1.4000

Table 8 shows the rate of rise of bilirubin for each percentiles in different time period as noted in the table maximum rise of bilirubin is noted at 12 to 24 hours interval and then the bilirubin rise slows down and it very minimal after 72 hours and the bilirubin level tends to fall after 108 hours.

FIGURE 14 RISE OF MEAN BILIRUBIN IN DIFFERENT TIME PERIOD



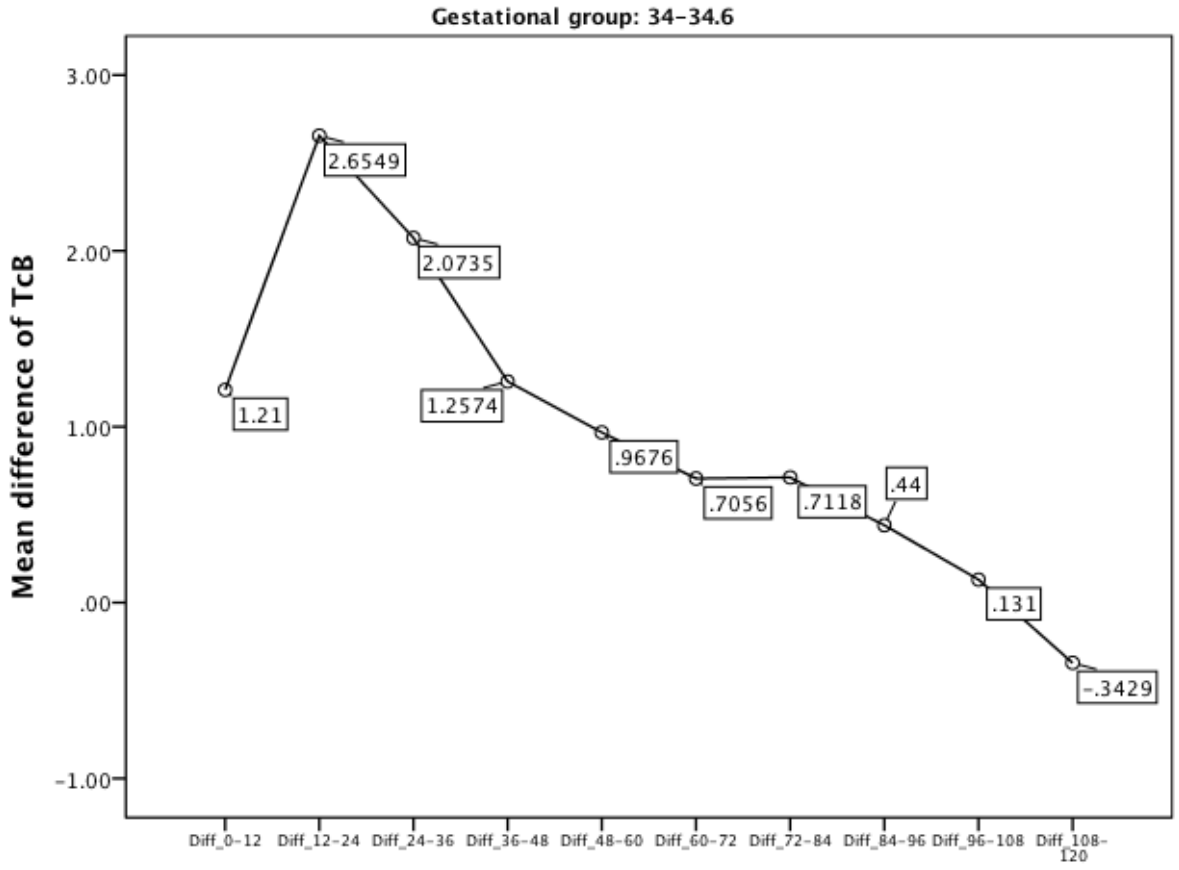
As shown in figure 14 maximum rise in bilirubin noted in the first 24 hour and then there is a gradual increase in bilirubin till 72 hours after which the rise of bilirubin is negligible. After 108 hours of life the figure shows actually a decline of serum bilirubin as shown by the negative value or rate of rise

TABLE 9 RISE OF MEAN BILIRUBIN IN DIFFERENT TIME PERIOD

Percentile	**Increase in TcB Level, mg/dl per h**									
	6-12	12-24	24-36	36-48	48-60	60-72	72-84	84-96	96-108	108-120
5th	0.033	0.075	0.025	0.01	-0.017	-0.05	-0.067	-0.075	-0.11	0.14
10th	0.05	0.117	.075	0.03	0.017	0.017	-0.33	-0.033	-0.79	0.116
25th	0.117	0.175	0.108	0.075	0.050	0.025	0.019	0.008	-0.033	0.060
50th	0.217	0.217	0.15	0.108	0.100	0.058	0.05	0.033	0.017	0.017
75th	0.3	0.258	0.216	0.15	0.133	0.100	0.083	0.075	0.058	0.041
90th	0.42	0.338	0.33	0.2	0.167	0.167	0.117	0.141	0.138	0.100
95th	0.43	0.383	0.41	0.217	0.278	0.221	0.15	0.167	0.188	0.117
Mean	0.225	0.217	0.176	0.108	0.094	0.067	0.05	0.043	0.018	-0.011

As shown in table 9 the mean rate of rise of bilirubin is maximum at 6 to 12 hours and is 0.225 mg/dl/hour.Rate of increase bilirubin remains high (0.217) in the next 12 hours .After 108 hours bilirubin starts falling as evident by negative mean TcB rise. The table also shows that the rate of rise of bilirubin is more than 0.25 mg/dl/hour in the babies ≥75 th percentile during the first 24 hours and ≥90th percentile at 24-36 hours.

FIGURE 15 RISE OF BILIRUBIN IN DIFFERENT TIME PERIOD FOR 34 WEEK NEW BORN



As shown in figure 15 maximum rate of riseof bilirubin is seen in the first 24 hours and there is a gradual increase after 24 hours till 72 hours after which the rate of rise of bilirubin is minimal .Figure shows a decline of bilirubin after 108 hours of life

FIGURE 16 RISE OF BILIRUBIN IN DIFFERENT TIME PERIOD FOR 35 WEEK NEW BORN

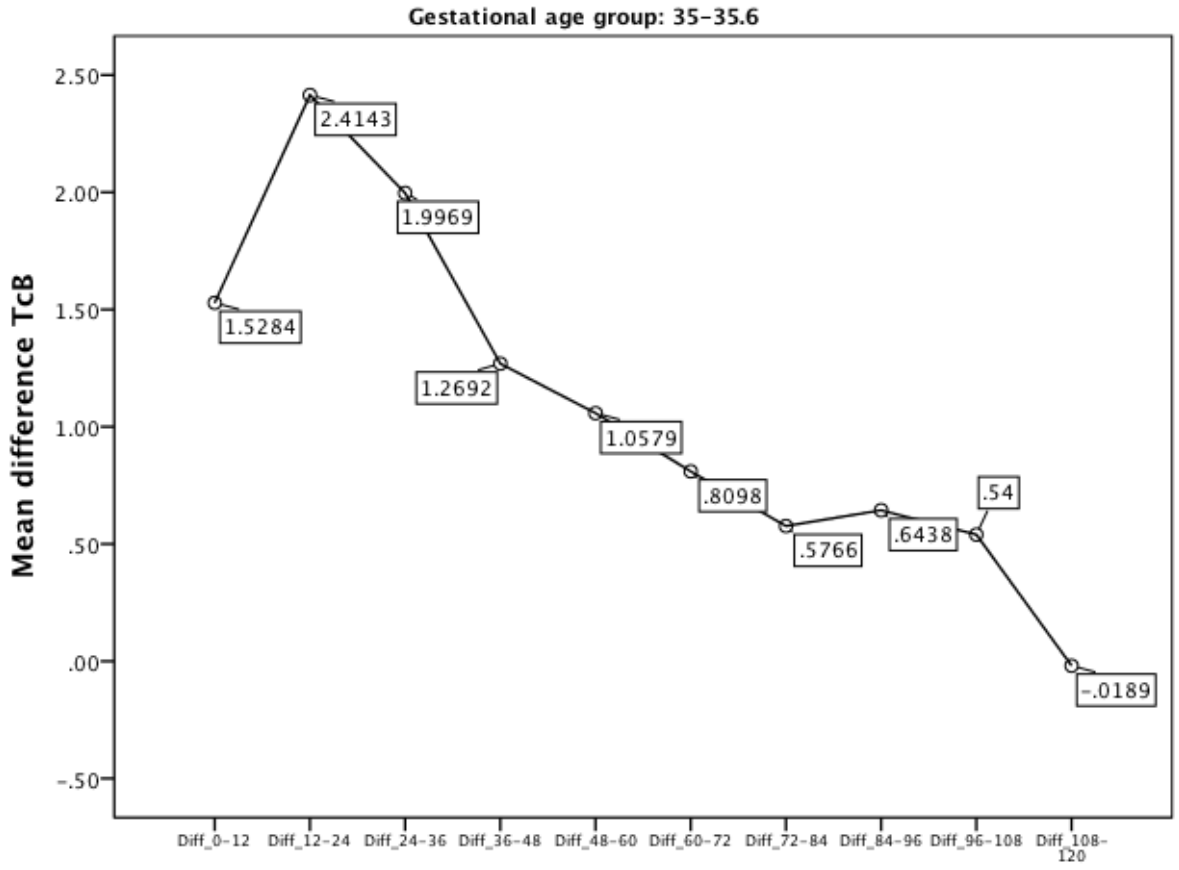


Figure 16 shows rise of bilirubin indifferent time period of a 35 week gestational age baby .The figure almost showed a similar pattern as a 34 week gestational age baby with peak rise of bilirubin in the first 24 hours then a slower rise of bilirubin till 72 to 84 hours after which the rise of bilirubin is insignificant.

FIGURE 17 RISE OF BILIRUBIN IN DIFFERENT TIME PERIOD FOR 36 WEEK NEW BORN

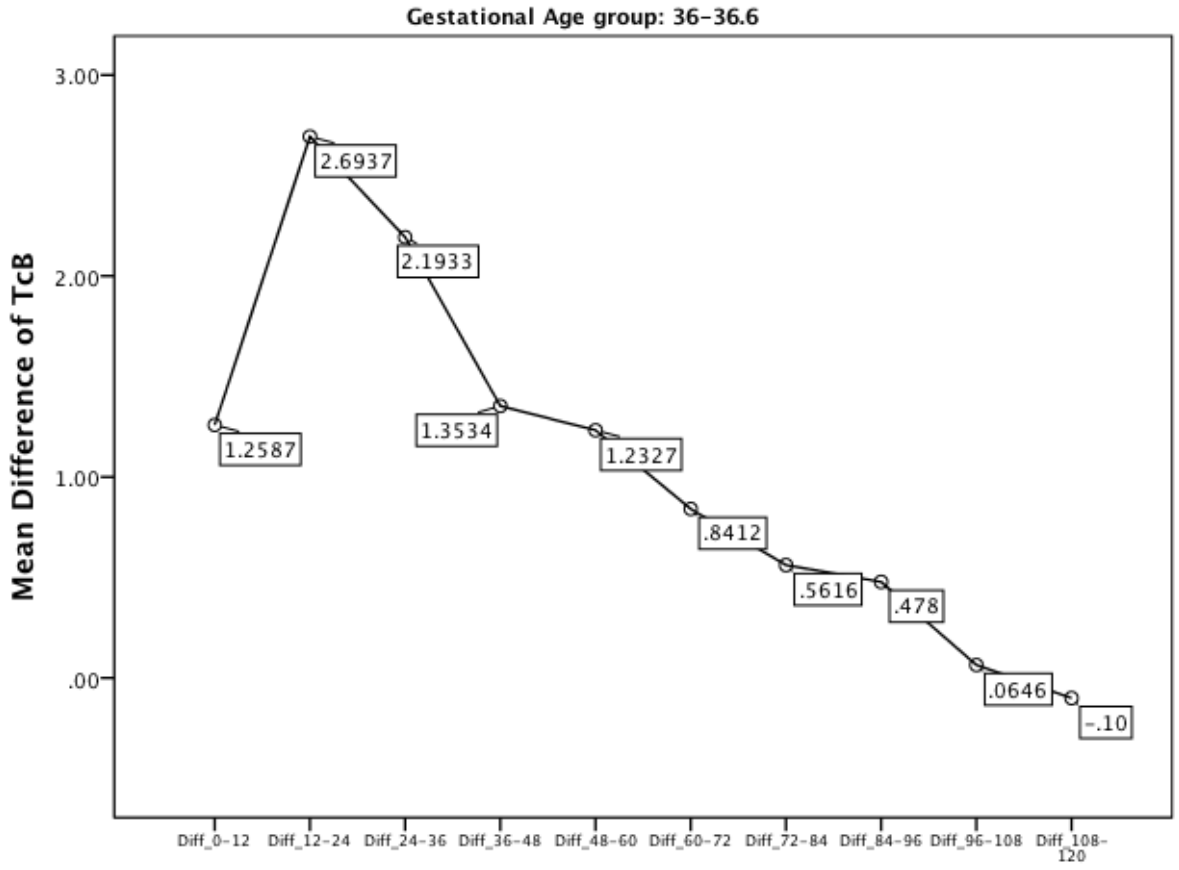


Figure 17 shows rise of bilirubin indifferent time period of a 36 week gestational age baby till 120 hours of life. The pattern of increase in bilirubin was similar to that of 34 and 35 weeks gestational age baby with peak rise of bilirubin in the first 24 hours then a slower rise of bilirubin till 72 to 84 hours after which the rise of bilirubin is insignificant. After 108 hours the bilirubin value actually starts declining.

TABLE 10RATE OF RISE OF MEAN TCB IN DIFFERENT GESTATIONAL AGE

Time	34 weeks		35weeks		36 weeks		P value
	Mean	SD	Mean		Mean	SD	
6 hours	2.69	0.97	2.91	0.8	2.84	0.98	0.327
12 hours	3.88	1.47	4.4	1.29	4.1	1.37	0.69
18 hours	5.2	1.47	5.8	1.43	5.4	1.43	0.233
24 hours	6.58	2.27	6.8	1.86	6.89	1.75	0.673
36 hours	8.6	2.1	8.78	2.08	8.95	2.13	0.783
48 hours	9.8	2.03	10.2	2.48	10.34	2.05	0.547
60 hours	10.3	2.9	10.9	2.56	11.44	2.33	0.088
72hours	11.1	2.28	11.71	2.26	12.22	2.21	0.082
84hours	11.6	2.03	11.87	2.27	12.67	2.2	0.047
96 hours	11.7	2.03	12.52	1.94	13.24	2.5	0.023
108hours	11.9	1.8	13.03	1.79	13.24	2.8	0.042
120hours	11.4	2.09	12.98	2.13	12.98	2.3	0.02

As shown in table 10 the rate of rise of bilirubin in the three gestational age considered (34, 35, 36 weeks) showed a similar pattern a maximum rise at 12 to 24 hours and an insignificant rate of rise after 72 hours. More over the mean bilirubin of the three gestational age did not statistically significant as shown by the P value by one way ANOVA test.

TABLE 11 CORRELATION BETWEEN TCB AND TB VALUE

		TB1	CospTCB
TSB	Pearson Correlation	1	.845
	Number of paired values analysed	102	102
TcB	Pearson Correlation	.845	1
	Number of paired values analysed	102	102

During the course of the study, paired serum bilirubin were taken during 102 episodes. The paired TcB and serum bilirubin values were analysed to see the correlation between them.

Table 11 shows the correlation between the TcB value and the paired serum bilirubin value obtained. The correlation coefficient between TSB and TcB was found to be 0.845 which is more closer to 1 and indicates a linear relation between the serum bilirubin and the Transcutaneous bilirubin value.

FIGURE 18 GRAPH SHOWING CORRELATION BETWEEN TCB AND TB VALUE

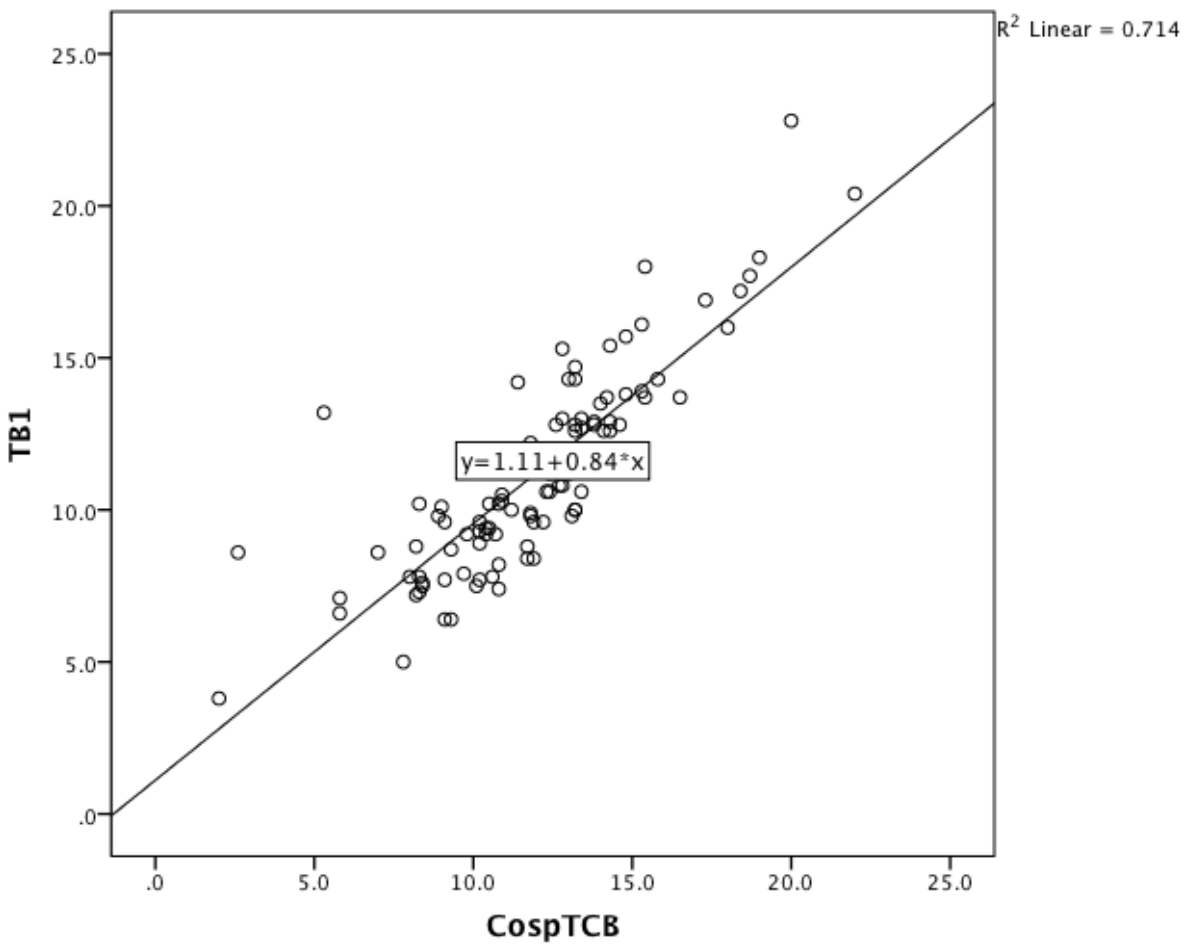


Figure 18 shows the graph depicting a linear relationship between the Total serum bilirubin estimated and the corresponding TcB. A total of 102 paired samples were obtained for comparison

FIGURE 19 BLAND ALTMAN PLOT:

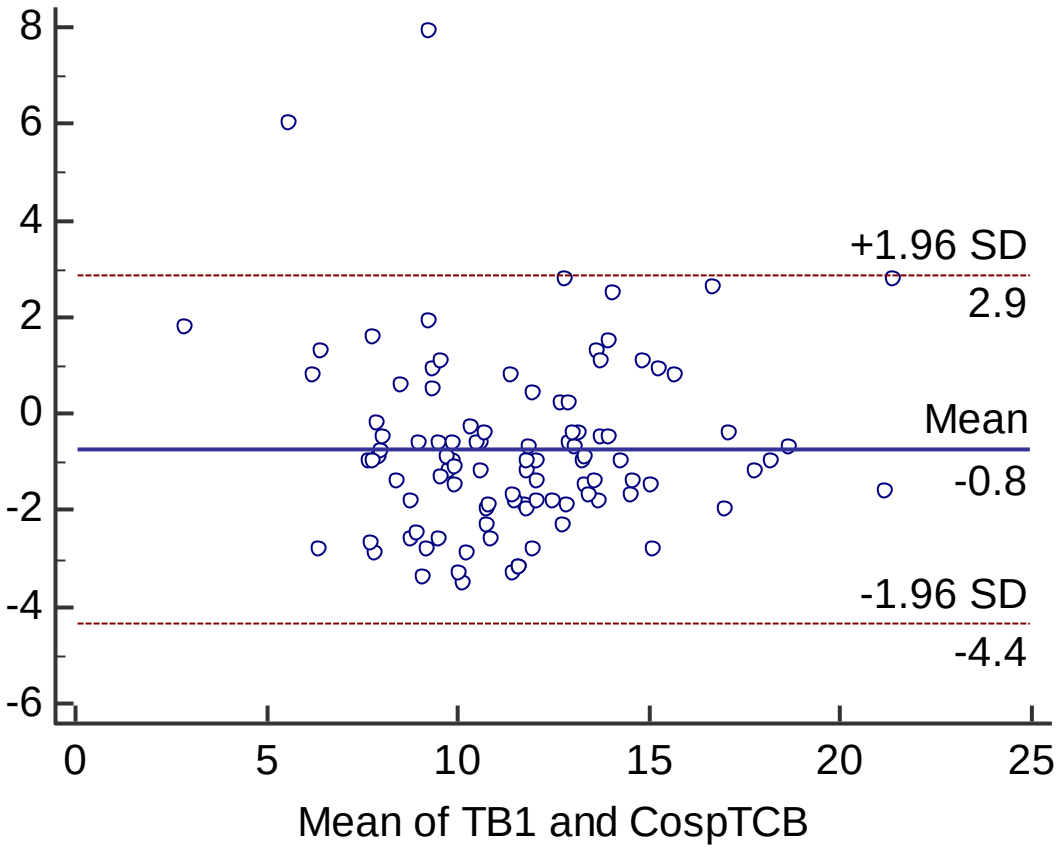


Figure 19 shows the Bland Altman plot showing the agreement between the TcB and the total serum bilirubin value as shown in the figure +1.96 standard deviation was 2.9 and -1.96 standard deviation was -4.4 which is not clinically acceptable.

REGRESSION FORMULA

From the paired serum and transcutaneous bilirubin values, we tried to construct a regression equation to estimate serum bilirubin level from any given TcB level. We derived the following equation:

Y= 1.11+0.84 X, where y represents serum bilirubin level and x represents TcB values.

DISCUSSION

Early identification of hyperbilirubinemia is essential as it provides a clear plan for discharge and also the follow up plan for early discharge babies especially if they are discharged before 72 hours of life in term babies. Neonatal hyperbilirubinemia is the most common cause of readmission to hospital in the newborn period. Pre-discharge bilirubin estimation for the prediction of subsequent hyperbilirubinemia is one of the preferred interventions to decrease future complications.. Serum bilirubin estimation for assessing the risk of hyperbilirubinemia needs invasive technique and in order to circumvent the invasiveness of serum bilirubin estimation, TcB measurement was introduced. Earlier TcB machines utilised limited wave length for assessing skin bilirubin level and hence melanin and haemoglobin levels interfered with the TcB estimation. Newer machines like BiliChekbilirubinometer and Draeger Jaundice Meter JM-103 are found to be uninfluenced by the colour of the skin or the haemoglobin level.

To assess the risk of hyperbilirubinemia using TcB values, TcB nomogram is a necessity as the nomogram using TSB cannot be applied for TcB values.

Most nomogram assessing the risk of future hyperbilirubinemia considers new born babies more than 35 weeks as a single group, when in reality late preterm babies are more prone to develop significant hyperbilirubinemia as compared to their term counterparts.

A literature search did not reveal any nomogram exclusively for late preterm babies. There are also very few nomograms for Indian populations. Hence the need to do the current study.

One published nomogram from Indian population was by Satish Mishra et al from the Department of Pediatrics, All India Institute of Medical Sciences, New Delhi. In the above mentioned study, the authors made it clear that the need for phototherapy was higher for late preterm as compared to term neonates and the difference was statistically significant with the proportion of preterm babies needing phototherapy amounting to 29 % and term babies needing phototherapy being 10 %.The study had only 10 % of babies in the late preterm group and the authors have raised their concern that with increasing rate of late preterm births, predictive ability of their nomogram would change .

While starting the study, we had anticipated that this study would differ from other studies in two crucial aspects.

The first was that we would recruit only late preterm babies, who constituted a small fraction of babies evaluated for constructing nomograms for newborn 35 weeks or above.

The second was the type of feeding. Since many of the studies were in term babies in the Western world, we assumed that this population in south India would have a greater proportion of breast fed babies.

During the study period, we recruited a total of 270 babies and followed them with serial TcB monitoring at 6 hour intervals in the first 24 hours and then 12th hourly till 120 hours. A total of 2109TcB values were

obtained.Otherstudiesinvolved in the construction of nomogram included all babies more than 35 weeks as a single group. In the study by SathishMisra et al,of the 625 babies evaluated,only 10% were late preterm. Only one study byDaniele De Luca et al constructed nomogram in babies more than 35 weeks recruiting a total of 2198 babies of whom 27% were 35 and 36 weeks. The issue with their nomogram was that, though they constructed a separate nomogram for babies born at 35 and 36 weeks, they did not include 34 weeks babies in their study. In their study, Maisels et al performed 9397 TcB measurements on 3984 healthy newborn infants more than 35 weeks of life from 6 to 96 hours of age; of the recruited patients, 17.2% of babies were born at a gestational age of 35 and 36 weeks, but none of these nomogram can be considered as representation of late preterm period.

As shown in Table 3, less than two-thirds of the babies in the study cohort were on exclusive breast feeds.In this study population by de Luca et al,80% of the babies were on exclusive breast feeds which is much higher as compared to our study group. Other studies from India just mention that most of the babies were breast fed and one study by M. Jeffrey Maisels et al reported exclusive breast feeding rate of 66%.Compared to other studies, our study had a lower percentage of babies with exclusive breast feeding which can be explained by the fact that we were dealing with a separate population of more immature babies than other studies.In the study by Satish Mishra et al,90 % of babies were term babies while in the study by De luca et al and in Maisel's study 66% and 83 % of babies were term respectively.All studies included babies from 35 weeks only. As we

were dealing with more preterm babies, exclusive breast feeding rate is also expected to be less. This is so, because late preterm have a greater incidence of feeding difficulties and also the fact that more of their mothers are likely to have medical/obstetric factors which precludes breastfeeding in the first few days of life.

About 49% of the babies were born by CS and rest 51 % were born by vaginal delivery; in comparison, Amarjeet S Wagh et al from south India, in a study comparing the morbidities of late preterm with term babies,found that CS accounted for 86.8% births and only 10.5% delivered by normal vaginal delivery. In our institution itself, the overall CS rate is between 25-30%.This difference may have a bearing on the bilirubin levels, as normal vaginal delivery is expected to be associated with early establishment of breast feeding and in late preterm babies delay in establishment of feed is an important cause of hyperbilirubinemia (as it leads to increased entero-hepatic recirculation). The increased CS rate in our cohort was probably because the obstetric indication for delivering the baby at a preterm gestation also necessitated a Caesarean section for maternal/ neonatal indications.

The mean weight of the new born babies recruited for the study was 2274 grams and the mean gestational age was35 weeks+ 6 days.

As shown in Table 4, among the late preterm babies assessed, more than half (51 % of babies) were born at 36 weeks, 27 % at 35 weeks and 23 % of babies at 34 weeks. We could not get an adequate representation for each gestation to

construct nomograms for each gestation if necessary.This may alter the nomogram in favour of 36 weeks babies.

As shown in Table 5,74% of our study population were appropriate for gestational age (AGA) as per Fenton'schart(10^{th} percentile taken as cut off),24 % were small for gestational (SGA) and only 2% were large for gestational age (LGA).Our cohort had a larger proportion of SGA babies than other studies. In the study by Satish Mishra et al almost 88% were AGA and only 4 % were SGA. In our study population there was a marked increase in the incidence of growth restriction, which may be because of more maternal complications like pregnancy induced hypertension, placental abnormality leading to growth restriction and severe growth restriction by itself leading on to early induction of labour . We have not however assessed the reasons of SGA within our cohort.

A total of 140 TcB values was needed as sample size for each epoch,but we could get only 130 TcB values at 120 hours of life because of time constraint and as many babies were discharged between 72 and 96 hours of life. A large number of babies were also taken off the study because they were started on phototherapy.Even with a sample size of 130, the confidence limit was 95% with an unit precision of 1 which is acceptable.

We recruited a total of 270 babies and a total of 2109 TcB values were measured among the recruited babies. Of the babies, about 20 % were 34 weeks 28% were

35 weeks and 52 % were 36 weeks .We separately analysed the gestational age distribution in each time epoch to see any marked difference in each time period but found almost the same proportion of representation were from each gestational age in each time epoch.

We longitudinally followed up the babies recruited in the study till 120 hours of life. In a large number of babies(51.45 %) TcB measurement could not be obtained till 120 hours of life as they were either discharged early or were started on phototherapy. In our study those babies started on phototherapy the pre phototherapy values were included in the study. This is in contrast to some of the earlier studies constructing TcB nomogram like the TcB nomogram by Satish Mishra et al ,Sanpavat et al where they excluded theTcB values of babies started on phototherapy. In the study byMaisels et al,which was a cross sectional study no baby on phototherapy was considered .We included the babies without haemolytic anemia in our study and we included the pre phototherapy value of babies started on phototherapy as we believed it represents the actual normative data and excluding the pre phototherapy value may lead to falsely low normative value.

In constructing the nomogram, we opted to longitudinally follow up babies at 12^{th} hourly interval till 120 hours of life with more frequent assessment in the first 24 hours .Most of the previous studies like the one by Maisels et al and Deluca et al constructed bilirubin nomogram till 96 hours of life and the one bySatish Mishra et alTcB nomogram was constructed till 72 hours of life

only.These studies involved a predominant number of term babies for whom nomogram till 96 hours of life is sufficientsince studies have shown that in term babies serum bilirubin peaks by day 3 and then falls, but for preterm babies the bilirubin peaks by around 5th day and then falls.

As bilirubin peak was expected in preterm babies by day 5 of life, we decided to follow up babies till 120 hours of life

Our nomogram did not show any marked increase in bilirubin after 72 hours and in fact a fall in bilirubin was seen after 108 hours of life. This may be attributed to the actual natural history of bilirubin rise in late preterm babies or may be because the babies in the higher percentiles being taken out of study due to start of phototherapyand babies in the lower percentiles being followed up till 120 hours.

A comparison of the centiles between our study and the two other studies showed almost similar mean TcB levels in each epoch until 72 hours. However, the 95th centile showed higher values in the CMCH study as compared to the studies by Misra et al and De Luca et al. This may be understandable given that late preterm were likely to have higher bilirubin levels as compared to term babies.

TABLE – 12 COMPARISON OF TCB VALUES OF OUR STUDYWITH TCB VALUES OF PREVIOUS STUDIES

Study	24 hours		36 hours		48 hours		60 hours		72 hors	
	50^{th}	95^{th}	50^{th}	90^{th}	50^{th}	90^{th}	50^{th}	90^{th}	50^{th}	90^{th}
CMCH Study	6	10.1	8.3	13.2	9	14.2	10	14.5	10.8	14
Daniele De Luca et al(35 &36 weeks)	5.8	9	6.7	10.8	8	13.8	8	14	8.8	15.4
Satish Mishra et al(97^{th} percentile)	5.8	9.2	7.8	11.5	9	12.3	9.8	14	14	10.2

When compared to De Luca nomogram for 35 and 36 weeks babies,our TcB obtained at 72 hours showed a marginally lower level. This may be due to differences in the policy of starting phototherapy since we can see that the levels until 60 hours in the CMCH study were higher. A higher incidence of hyperbilirubinemia (and values in the upper ranges of physiologic jaundice) is expected in our cohort given that we were dealing babies at lower gestational age and the fact that we were dealing with Asian population who are known to be more prone for hyperbilirubinemia. Therefore, it is more likely that more babies in our cohort with upper ranges of TcB were started on phototherapy after 60 hours of age and were thus excluded from further evaluation.

The mean TcB values of boys and girls were obtained with 140 boys and 130 girls being involved in the study but it was seen that there was no significant

difference between the TcB values obtained from the boys and girls in this cohort; hence the need of separate nomogram is questionable.

The rates of TcB levels increase for different hours of life and percentiles are particularly useful in the light of current guidelines of AAP which recommend more attention to those babies with bilirubin increasing at rates>0.25 mg/dL/h. Age-specific rate of rise in STB or TcB is a reasonably predictable surrogate for requirement of phototherapy in neonates. In our study, rate of rise of bilirubin more than 0.25 mg/dl/h was noticed for the first 24 hours in ≥ 75^{th} percentile group and after which noticed in babies ≥90^{th} percentile till the 36^{th} hour of life. After 36 hours, the rate of rise of bilirubin does not cross this value. Thus, any late preterm baby above the 75^{th}centile of this nomogram would need to be evaluated in the first 24 hours and any baby above 90^{th}centile between 24-36 hours and probably thereafter.

In the nomogram of Satish Mishra et al, rate of rise in TcB of >0.25mg/dL/h was present only during first 24 hours of age in ≥90th percentile curves while in the nomogram constructed by De luca et al found that the mean rate of rise is lower than 0.25 mg/dl/h for all the percentiles.They also noted that if a baby 'crosses' the curves, rate of rise of Tcb is expected to be more than 0.25 mg/dl/h .

Rate of rise of bilirubin is maximum during the first 24 hours of life (with the maximum rate of rise being between 6-12 hours)after which there is a gradual decrease in rate of rise. Bilirubin level gradually rises till 72 hours of life after

which the rate of rise is almost negligible and after 108 hours bilirubin level actually starts declining.

Rate of rise of TcB value was estimated separately for the three gestational ages in our study group; 34, 35 and 36 weeks. The general pattern of rate of rise of serum bilirubin and the rate of rise in the three gestational group did not show any significant difference which implies that late preterm babies may be considered as a single group while considering the construction of nomogram.

The correlation between TcB values and the paired serum bilirubin estimated as part of unit policy was estimated as the secondary outcome of the study .The correlation coefficient between the TcB and the corresponding TSB was found to 0.825 which is acceptable. As seen in the graph there is a linear relation between TcB and the corresponding TSBvalue.

A Bland-Altman plot was then done to see the agreement between the TcB values and the TSB values. According to the Bland-Altman plot, +1.96 standard deviation was 2.9mg% and -1.96 standard deviation was -4.4mg% which is not clinically acceptable. In our study, while the correlation was good, the difference between the two values was too large to be acceptable clinically.

We tried to evolve a regression formula for calculating serum bilirubin level from the TcB value obtained

REGRESSION FORMULA:

$$Y = 1.11 + 0.84\ X$$

Where y stands for total serum bilirubin level and X stands for transcutaneous bilirubin obtained. This regression equation will now need to be validated prospectively in a larger, different population before considering it for clinical use.

CONCLUSION

1.Transcutaneous bilirubin nomogram was constructed for a cohort of late preterm babies. The 5th, 10th, 25th, 50th,75th,90th,95th percentiles TcB charts were created

2.Rate of rise of bilirubin is maximum during the first 24 hours of life after which there is a gradual decrease in rate of rise. Peak bilirubin level in this cohort is at 72 hours of life.

3.Rate of rise of bilirubin more than 0.25 mg/dl/h (which is a predictor of hyperbilirubinemia) was noticed for the first 24 hours in ≥ 75th percentile and in values ≥90th percentile till the 36th hour of life.

4. There is no significant difference between the nomogram for boys and girls and also not much variability was noted in the rate of rise of bilirubin for 34,35 and 36 weeks babies hence they may be taken as a single group in the construction of TcB nomogram.

5. There exists a good correlation between the TcB value and the paired TSB obtained though the agreement is not very good.

LIMITATION

1. It is not a population based study.

2. Percentile curves have not been prospectively validated for prediction of subsequent hyperbilirubinemia.

3. Study population was mainly south Indian babies and hence may not be universally applicable.

4. Because of time constraints and non-availability of babies satisfying entry criteria, we could not achieve the sample size at 108 and 120 hours.

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ஒப்புதல் அறிக்கை

தலைப்பு: பிரசவ காலத்திற்கு சில நாட்களுக்கு முன் பிறந்த குழந்தைகளுக்கு உண்டாகும் மஞ்சள்காமாலை (ஹைப்பர் பிலிருபினீமியா) நோயை முன்னரே கணிப்பதற்கு டிரான்ஸ்குடேனியஸ் பிலிருபின் அளவுகள்.
(டிரான்ஸ்குடேனியஸ் பிலிருபின் நார்மோகிராம் இன் லேட் ப்ரீடெர்ம் பார் பிரிடிக்ஸன் ஆப் ஸிக்நிபிகன்ட் ஹைப்பர் பிலிருபினீமியா)

ஆய்வில் தன்னிச்சையாக பங்கேற்பதற்கு அழைப்பு

மஞ்சள் காமாலை பச்சிளங்குழந்தைகளுக்கு ஏற்படும் ஒரு பொதுவான பிரச்சனையாகும். நிலையான பிரசவகாலத்தில் பிறந்த குழந்தைகளில் 67 சதவீத குழந்தைகளுக்கும் கிட்டத்தட்ட குறை பிரசவத்தில் பிறந்த எல்லா குழந்தைகளுக்கும் பிறந்த முதல் வாரத்தில் மஞ்சள் காமாலை ஏற்படுகிறது. குறை பிரசவத்தில் பிறந்த குழந்தைகளுக்கு நிலையான பிரசவகாலத்தில் பிறந்த குழந்தைகளை விட மஞ்சள் காமாலையின் அளவு அதிகமாக இருக்க அதிக வாய்ப்புள்ளது. சில குழந்தைகளுக்கு பல்வேறு காரணங்களால் மஞ்சள் காமாலையின் அளவு அதிகமாக இருக்கிறகு இதற்கு சிகிச்சையளிக்கவேண்டும். மஞ்சள் காமாலையை குறைப்பதற்கு குழந்தைகளை மின்சார குழல்விளக்கின் ஒளி (போட்டோதெரபி) படும் படி வைப்பதே சிகிச்சையாகும். அரிதாக சில நேரங்களில் மஞ்சள் காமாலையின் அளவு அதிகமாக இருக்கும் போது குழந்தைக்கு இரத்தத்தை மாற்றுவதன் மூலம் சிகிச்கையளிக்கப்படுகிறது. குறிப்பிட்ட அளவு வரை மஞ்சள் காமாலை இருப்பது ஆபத்தில்லை, ஆனால் அந்த அளவை விட அதிகமனால் அது குழந்தையின் மூளையை பாதித்து மூளை வளர்ச்சியை பாதிக்கும்.

மஞ்சள் காமாலை இரத்தத்தில் உள்ள பிலிரூபின் எனப்படும் பொருளால் உருவாகிறது. தற்போது மஞ்சள் காமாலையை சீர்படுத்த இரத்த மாதிரிகளை எடுத்து பிலிரூபின் அளவை கண்டு அதிகமாக இருந்தால் போட்டோதெரபி அளித்து மீண்டும் மீண்டும் பிலிரூபின் அளவு குறையும் வரை பரிசோதிக்கவேண்டும். இதற்காக குழந்தைக்கு பலமுறை ஊசிகுத்தவேண்டியிருக்கிறது.

தற்போது புதிய கருவிகள் கண்டுபிடிக்கப்பட்டுள்ளன இதனால் தோலின் மேற்பரப்பில் ஒரு ஒளியை செலுத்தி அதன்மூலம் பிலிரூபின் அளவை சோதிக்க முடியும். இது குழந்தைக்கு பலமுறை ஊசிகுத்தி இரத்த மாதிரி எடுக்கவேண்டியதை குறைக்கும். ஆனாலும் இந்திய குழந்தைகளின் தோலில் உள்ள சாதாரண அளவு பிலிரூபின் எவ்வளவு என்பது நமக்கு தெரியாது ஆதலால் எந்த அளவு பிலிரூபின் இருக்கும் போது சிகிச்சை தொடங்கவேண்டும் என்பது கவலையளிக்கிறது. எனவே இந்த ஆய்வு மூலம் கருவுற்று 34-36 வாரத்தில் பிறந்த இந்திய குழந்தைகளின் தோலின் பிலிரூபின் அளவை சோதனை செய்து சாதாரணமாய் இருக்கக்கூடிய பிலிரூபின் அளவை கண்டுபிடிக்க இருக்கிறோம்.

உங்கள் குழந்தைக்கான சிகிச்சைமுறை எங்கள் மருத்துவமனையின் நடைமுறைகள் படி தொடர்ந்து வழங்கப்படும். குழந்தையின் தோலின் பிலிரூபின் அளவு அதிகமாக இருப்பதாக தெரியவந்தால் அது இரத்தப்பரிசோதனையின் மூலம் உறுதிசெய்யப்படும்.

இந்து ஆய்வு எவ்வாறு செய்யப்படுகிறது?

குழந்தையின் அடிப்படை தகவல்களுடன் மஞ்சள் காமாலை ஏற்படுவதற்கான காரணிகள் ஏதாவது இருந்தால் குறிப்பெடுக்கப்படும். டிரான்ஸ்குடேனியஸ் பிலிருபின் அளவுகள் குழந்தை பிறந்த முதல் நாளில் முதல் 6-8 மணி நேரத்திற்குள்ளும் மற்றும் ஒவ்வொரு 6 மணிநேரத்திலும், அதன் பின் 4-5 நாட்களுக்கு ஒவ்வொரு 12 மணி நேரத்திற்கும் பரிசோதிக்கப்படும். இது எங்களுக்கு பிரசவ காலத்திற்கு சில நாட்களுக்கு முன் பிறந்த இந்திய குழந்தைகளுக்கு மஞ்சள் காமாலையின் சாதாரணமான மற்றும் அதிக அளவை தீர்மானிக்க உதவும்.

உங்கள் குழந்தைக்கு அதிக அளவான மஞ்சள் காமாலைக்கு போட்டோதெரபி சிகிச்சை தேவைபட்டால் தோல் அளவு பரிசோதனை நிறுத்தப்பட்டு நிலையான நடைமுறைகள் படி சிகிச்சையளிக்கப்படும்.

தகவல்கள் இரகசியமாக வைக்கப்படுமா?

உங்களை பற்றியும் உங்கள் குழந்தையை பற்றியும் இந்த ஆய்வின் போது பெறப்படும் தகவல்கள் அனைத்தும் பாதுகாப்பாக இரகசியமாக வைக்கப்டும். உங்களின் மருத்துவ பதிவேடுகளை ஆய்வில் ஈடுபடும் நபர்கள் உங்களின் முன் அனுமதியின்றி பார்க்க முடியும்.

நீங்கள் உங்கள் குழந்தையை எப்பொழுது வேண்டுமானாலும் இந்த ஆய்விலிருந்து விலக்கிக்கொள்ளலாம. உங்களை பற்றிய தகவல்கள் ஆய்விலிருந்து நீக்கப்படும். இந்த ஆய்வு இம்மருத்துவமணையில் வழங்கப்படும் பச்சிளங்குழந்தைகளுக்கான சாதாரணமான கவனிப்பில் கூடுதல் ஆகும். எனவே ஆய்வில் சேர்ப்பதற்கு மறுத்தாலும் இந்த பச்சிளங்குழந்தைகள் பிரிவில் கடைபிடிக்கப்படும் நெறிமுறைகள் படி உங்கள் குழந்தைக்கு சிகிச்சை அளிக்கப்படும்..

உங்கள் குழந்தையை இந்த ஆய்வில் சேர்ப்பீர்கள் என்று நம்புகிறோம் அவ்வாறாயின் உங்களை ஒப்புதல் படிவத்தில் கையொப்பமிடுமாறு கேட்டுக்கொள்கிறோம்.

உங்களுக்கு இந்த ஆராய்ச்சி பற்றி வேறு கேள்விகள் கேட்க வேண்டியிருப்பின் கீழ்கண்ட மருத்துவர்களில் யாரையாவது தொடர்பு கொள்ளலாம்.

Transcutaneous bilirubin normogram in late preterm for prediction of significant hyperbilirubinemia

Patient information sheet

Invitation to participate voluntarily in a study

Jaundice is a common problem in the new born period. About 67% of babies born at term gestation and almost all premature infants develop jaundice in the first week of life. Premature babies are more likely to have a higher level of jaundice than babies born at term. Some babies develop a higher than normal level of jaundice due to various reasons and this requires treatment. Treatment to reduce jaundice is by keeping the baby under coloured lights (called phototherapy) or rarely by changing the baby's blood in very high jaundice. Jaundice upto a certain limit is not dangerous but if it exceeds a certain limit it can cross to the brain and cause damage to the developing brain .

Jaundice is caused by the presence of a substance called bilirubin in the blood. Currently the management of jaundice is to check blood sample for bilirubin level (for those newborn whose jaundice looks to be higher than normal) and if found high, start with phototherapy light and recheck blood bilirubin level few times until it comes down to a safe level. This may require multiple pricks.

Newer instruments have come up, which can check bilirubin from the skin surface by shining a light on the skin. This might decreases the need for blood sampling. But we yet do not know properly what the normal jaundice levels are in the skin of Indian preterm newborn and when we should be worried enough to start treatment and this study is thus done to find out the normal skin bilirubin levels in Indian babies born just before term gestation (at 34-36 weeks) so that we can find out higher levels by skin levels in the future.

The treatment of your baby will entirely be followed as per the practice in our hospital and if skin bilirubin value is found to be high, we will reconfirm it with blood value estimation .

How will the study be conducted?

The basic information of the baby along with any predisposing factors for the development of high jaundice will be noted .Transcutaneous bilirubin measurement will be done at 6 -8 hours of life and then every 6 hours in the first day and then every 12 hours for the next 4-5 days or time of discharge .This is will help us to determine normal and high jaundice levels in the first few days of life in Indian late preterm babies.

If your baby requires treatment for high jaundice with phototherapy, then the skin levels will be stopped and the treatment will be continued as per standard practice.

Protection of privacy

All information that is collected about the mother and baby will be treated in confidence. Only the investigators of this study will have access to the recordings.

You can withdraw from the study at any time. Information about the mother /baby will then be deleted. This study is in addition to normal neonatal care at the hospital. The baby will therefore be examined and followed up in accordance with normal procedures, even if you do not take part in the study.

We hope you will consent to be included in the study. In this case, we request you to sign the consent form.

If you have any questions about the study, please contact:

Dr.Santhanam Sridhar S OR Dr.Nelby George mathew
Neonatology Departments
Christian Medical College, Vellore 632004
0416-2286185, 0416-2283311

CONSENT FORM

BABY'S NAME

HOSPITAL NUMBER:

Title: Transcutaneous bilirubin nomogram in late preterm for prediction of significant hyperbilirubinemia.

Name of Researcher: [redacted]

I confirm that I have read and understand the information sheet for the above study and have had the opportunity to ask questions.

I understand that the participation of my baby in this study is voluntary and that I am free to withdraw my baby from the study at any time, without giving any reason, without the medical care or legal rights of my baby being affected.

I understand that sections of any of the medical notes of my baby may be looked at by responsible individuals from the study organisers or from regulatory authorities where it is relevant to my baby taking part in research. I give permission for these individuals to have access to the records of my baby.

I agree for my baby to take part in the above study.

Name of Parent:	Name of doctor:
Signature:	Signature:
Date:	Date:

Study Proforma

Title: "Transcutaneous bilirubin nomogram in late preterm for prediction of significant hyperbilirubinemia"

Study ID No: Baby's Hospital No: Mother's Hospital No:

Name: Gender:

Gestational Age: By LMP: By Dubowitz:

Birth weight:

Date of birth: Time of birth:

Mother's Blood Group ICT

Baby's Blood Group DCT

Reticulocyte count: _____ Blood picture-

G6PD-

Feeding Pattern:

1. Exclusive Breast feeding 2. Breast Feeding+ Artificial feeds
3. Artificial feeds 4. IV fluids

Medications: 1. _____

2. _____
3. _____
4. _____

Hours	TcB	SB
6		
12		
18		
24		
36		
48		
60		
72		
84		
96		
108		
120		

Abbreviations

AGA: Appropriate for gestational age

AAP:American academy of paediatrics

CO:Carbon monoxide

GA: Gestational Age

HPLC:High pressure liquid chromatography

RBC:Red blood cells

SGA: Small for gestational age

TcB: Transcutaneous Bilirubin

TSB:Total Serum Bilirubin

UGT1A1: uridine diphospho gluconurate glucoronosyl transferase 1A1